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ABSTRACT

This conference was designed to facilitate an exchange of information and experiences on the major issues in research with human subjects. In each session, a speaker from the United States and one from the United Kingdom reviewed procedures, progress, and problems related to a particular topic, leading to a thorough discussion of the advantages or disadvantages of the systems being compared. Each presentation thus provided a significant review of the topic under discussion. The following topics were presented: (1) Inititating Large-Scale Clinical Trials; (2) Randomized Controlled Trials in Health Services Research; (3) Problems of Long-Term Recordkeeping; (4) Compensation of Research Subjects for Adverse Effects; (5) Clinical Research on Children; (6) Role of the Public in Monitoring Research with Human Subjects; (7) Relationship Between Government and Industry in Clincal Trials; (8) International Standards in Clinical Research; and (9) Acceptance of Foreign Data by the Food and Drug Administration. Participants agreed that many benefits would result from the establishment of international standards for clinical research, not the least of which would be the possibility of objective and realistic comparison of data developed in either country and a simplification of procedures involved in licensing new products. (RL)

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Issues in Research With Human Subjects

U.S. DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

TM 810 275

ISSUES IN RESEARCH WITH HUMAN SUBJECTS

A SYMPOSIUM SPONSORED BY

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PREFACE

Clinical research studies are vital to the development of new medical procedures and new drugs and biologics used for the prevention, diagnosis, and treatment of disease. Such studies involve a variety of individuals and organizations: research investigators (including medical practitioners and statisticians), industrial and funding organizations, regulatory agencies, and the public. There is the obvious concern that the study design be scientifically adequate, but planners must consider a number of other aspects. The first is the necessity of the study; then further decisions must be made on the length of the study, a system of recordkeeping, recruitment of subjects, the use of children or other special study groups, and compensation for injured subjects. The public's role in planning, approving, and monitoring clinical studies must be kept in mind, particularly in light of the growing issues regarding ethical aspects of research.

Although the elements of clinical studies are common to all countries, the ease and security with which they are handled varies. Different laws, procedures for conducting studies, and health service delivery systems in different countries influence the experience and success rates of clinical trials.

This conference was designed to facilitate an exchange of information and experiences on the major issues in research with human subjects. In each session, a speaker from the United States and one from the United Kingdom reviewed procedures, progress, and problems related to a particular topic, leading to a thorough discussion of the advantages or disadvantages of the systems being compared. Each presentation thus provided a significant review of the topic under discussion.

In a final session, international standards for clinical research were considered. Although no conclusions were reached, participants agreed that many benefits would result from the establishment of such international standards, not the least of which would be the possibility of objective and realistic comparison of data developed in either country. Such standards would also simplify the procedures involved in licensing new products.

This volume reports the ways in which the United States and the United Kingdom handle some important ethical and administrative problems in the conduct of clinical research.

INTRODUCTION

Thomas E. Malone

To address "Issues in Research with Human Subjects" is an exceedingly complex task. There is, more than ever, the necessity for clinical research as a vehicle for controlled human testing of results before they are put into practice. In fiscal year 1975, the National Institutes of Health (NIH) inventoried its clinical trials and found that it was spending $115 million for more than 700 projects. It seems clear that, in the future, the NIH and the scientific community will assume increased responsibility for the effect of research on the quality and cost of health care. Accordingly, formal procedures for the identification and validation of relevant clinical research knowledge are being developed.

Second, this symposium represents a clear commitment by scientists to operate within the confines of new ethical, legal, and social imperatives. This is not to say that science has not always been anchored in these areas. But the ascending power of science has greatly exaggerated our responsibilities to its benefactors and patrons. The human consequences of modern biomedical research and technology—the control of fertility, surrogate organs, behavior modification, and the tremendous possibilities of genetic engineering, among others— have removed us from relative privacy and autonomy to an era of greater public scrutiny and participation in the affairs of science. Political and legal institutions have responded with regulatory constraints catalyzed by an ever-growing body of petitioners. Amidst some real and imagined threats to man and this planet, more than a dozen bills for the control and regulation of recombinant deoxyribonucleic acid (DNA) research have been introduced in the U.S. Congress. The instruments of governance will obviously be best served by the open, self-regulatory machinery being set in motion by this meeting

The first modern codification of biomedical ethics dates from 1803, when Thomas Percival was asked to draw up such a code for the Manchester Infirmary in England. First called "Medical Jurisprudence," the title was changed to "Medical Ethics," apparently the first use of the phrase. The code consists of 57 precepts requiring the physician to "unite *tenderness* with *steadiness* and *condescension* with *authority*" and to treat females "with the most scrupulous

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delicacy." Women's liberation was evidently unheard of, but the need for research was not. Precept XII states: "Whenever cases occur, attended with circumstances not heretofore observed, or in which the ordinary modes of practice have been attempted with success, it is for the public good . . . that *new remedies* and *new methods* of *chirurgical treatment* should be devised. But in the accomplishment of this salutory purpose, the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well-authenticated facts. And no such trials should be instituted without a previous consultation of the physicians or surgeons according to the nature of the case."

This document appears to have been the first plea for group consideration in medical research. The code imposes no duties or responsibilities on the Manchester Infirmary as an institution; it is addressed solely to the "gentlemen of the faculty," to individual physicians. That is where the responsibility rested for the next 150 years.

The first American Code of Medical Ethics was presented in the proceedings of the National Medical Convention in 1846-1847.

Two notable recommendations were included:

> (1) *It is a delicate and noble task, by the judicious application of Public Hygiene, to prevent disease and to prolong life; and thus to increase the productive industry, and. . .to add to the civilization of an entire people.* Here we begin to see the justification for clinical research and its connection to the values and the morals of a people.
>
> (2) *Too frequently we meet with physicians who deem it a venial error, in ethics, to permit, and even to recommend, the use of quack medicine or secret compounds by their patients or friends. They forget that their toleration implies sanction of a recourse by people generally to unknown, conjectural fashions of medication, and that the credulous in this way soon become the victims of an endless succession of empirics.* This comment could have been written with the Laetrile controversy in mind.

Toward the 1950's, a few American institutions recognized that group review was more practically treated as an institutional responsibility. When the NIH Clinical Center opened in 1953, Jack Masur, its first Director, instructed each Institute Director to establish a committee to review clinical projects that involved "unusual hazard." In certain circumstances, these committees were to refer projects to the Clinical Research Committee of the Medical Board "to investigate the scientific and ethical propriety" of the proposed procedure.

Although the relationship between the Institute committees and the Medical Board has changed from time to time, the system is still intact.

In 1966, all NIH grantees and institutions were required to establish what are now known as Institutional Review Boards. In following years these requirements were extended first to the entire Public Health Service (both with respect to grants and contracts) and then to the entire Department of Health, Education, and Welfare (HEW). Similar policies have been adopted by several Federal agencies, and many more use the Institutional Review Board without specific reference to HEW regulations.

These boards have not been required to address themselves to medical care as distinguished from medical research. In fact, present regulations distinguish between subjects at risk who are involved in research and those who are exposed only to the standard and accepted practices of medicine. This has had some unfortunate consequences. For example, to some people "ethics" is a problem related solely to organized research; and the doctrine of informed consent pertains only to research subjects, not patients. In addition, there is the gray area of "innovative medicine," in which departures from standard and accepted practice are made in the presumed interests of individual patients.

It is unfortunate but true that much of the current progress in protecting the rights of patients and subjects resulted from abuse. The modern era of biomedical ethics originates in the tragic revelations of Nuremberg. The development of the Public Health Policy for Protection of Human Subjects followed allegations of the transfer of live cancer cells to patients without their consent, and the first codification of the HEW regulations followed publicity concerning the Tuskegee syphilis studies.

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was created in 1974, occasioned by allegations of abuses in both the practice of medicine and in medical research. To date, the Commission has issued reports on fetal research, psychosurgery, research involving prisoners, research involving children, and research involving the institutionalized mentally infirm. Additional reports concerning the social, legal, and ethical dimensions of both research and practice are expected.

Science and scientific research know no national boundaries. Progress benefits all; abuse tarnishes everyone. For example, the report of the British Peel Committee was a forerunner of the American report on fetal research. The recent code on the Rights of the Sick and the Dying adopted by the Parliamentary Assembly of Europe in 1976 follows newspaper accounts of the technological ability to maintain vital functions in persons when their disease or injury is otherwise certainly fatal and irreversible.

The two countries have a great stake in working together. Necessary steps to protect the rights and well-being of patients and research subjects should be taken *before* tragic mistakes or abuses occur, rather than afterward. At the same time, regulation must not stifle innovation.

Part 1

INITIATING LARGE-SCALE CLINICAL TRIALS

Robert I. Levy and Edward J. Sondik

The extensive resources required by large-scale clinical trials and their potentially great impact on medical practice and on future research require that the decision to undertake a particular clinical trial be analytical and deliberate. This chapter focuses on the process of initiating clinical trials in the National Heart, Lung, and Blood Institute, outlining the Institute's decision and management process and emphasizing the rationale the Institute uses to undertake a trial. Two recent examples of the application of the process are discussed: a trial on drug treatment for mild hypertension, which was considered and rejected by the Institute; and a trial on the effect of beta-blocker drugs to combat postmyocardial infarction mortality, a trial now under way.

Introduction

Large-scale clinical trials play an important role in medical research and public health. The clinical trial provides the definitive validation step to test the efficacy of preventive and treatment regimens before they are introduced into practice (figure 1). Some trials require only a few patients in a straightforward experimental design, others use thousands of patients in a multifactorial statistical design. The large-scale clinical trial involves three or more clinical centers and over several hundred patients. For the National Heart, Lung, and Blood Institute (NHLBI) they can involve over 40 clinical centers, more than 10,000 subjects, and require up to 10 years to complete at costs over $100 million.

Because of the nature of coronary heart disease, where event rates occur on the order of 1 in 100 per year for the average individual, many of the trials of the NHLBI require extensive numbers of patients and clinical resources to complete. With its limited resources, the Institute carefully commits its resources to such trials, aiming at making the trials maximally cost effective. Although more detail on the entire decision-making process is available in reference 1, this chapter focuses on the earliest part—the genesis of a trial and the Institute's primary decision to commit resources to it. A particular focus is the rationale the Institute uses to decide to undertake a trial. Two illustrations of this decision-making process are discussed—a trial on drug treatment for mild hypertension, which was considered and rejected by the Institute, and a

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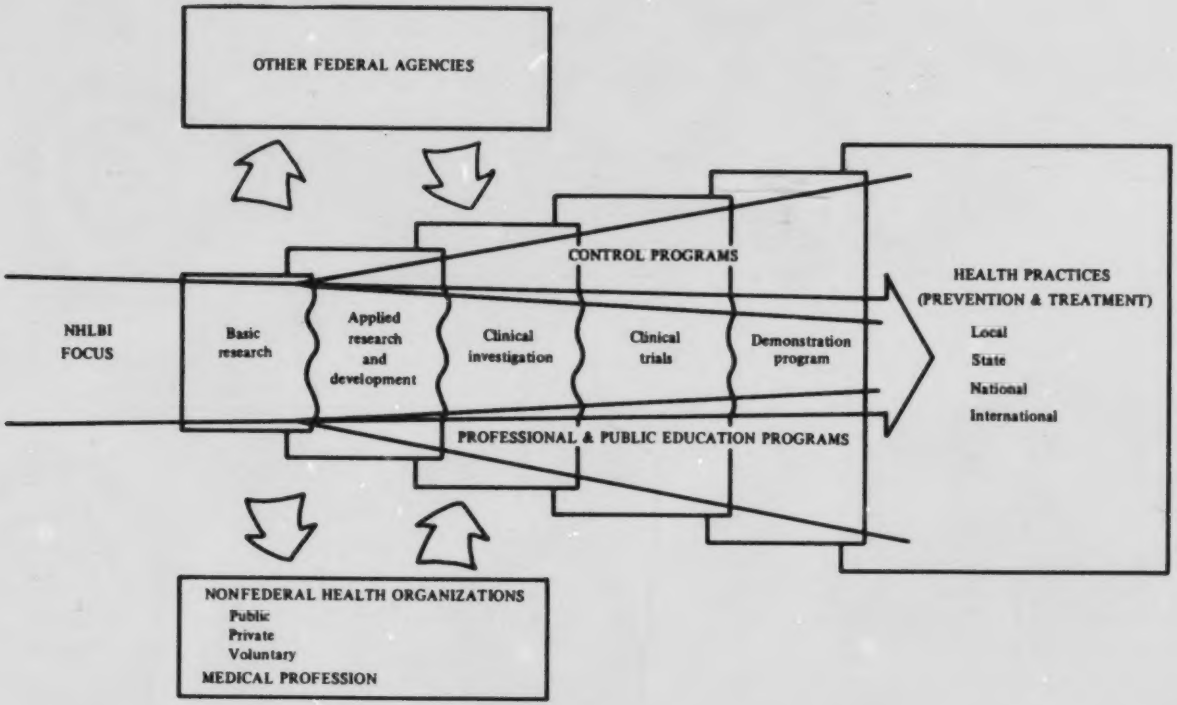

FIGURE 1. The flow from research to application

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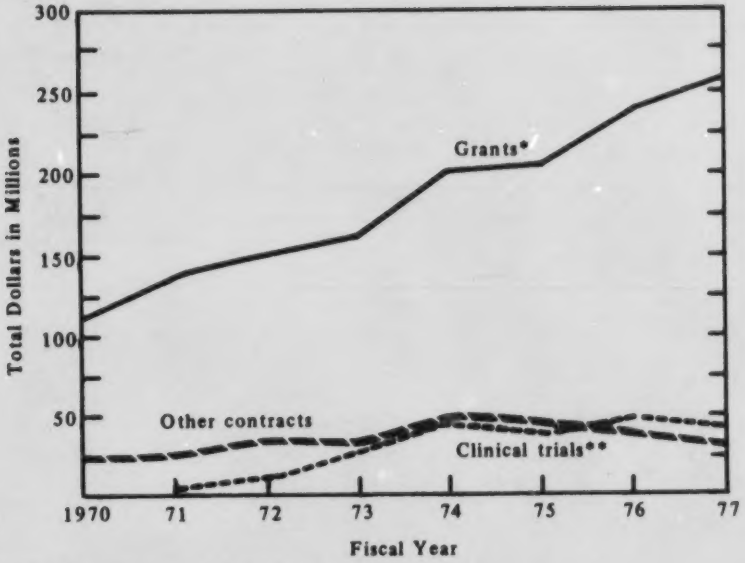

*Includes all research and training grants

**Major clinical trials: AMIS, CASS, CPPT, HDFP, MRFIT, BHAT

FIGURE 2. NHLBI extramural research funding, FY 1970 - 77

trial on the effect of beta-blocker drugs to combat postmyocardial infarction mortality, a trial now under way.

Clinical Trials in the National Heart, Lung, and Blood Institute

The NHLBI has extensive large-scale clinical trials dealing with critical issues in the prevention and treatment of heart, lung, and blood diseases. These contract programs now constitute about 15 percent of the Institute's extramural budget (figure 2). The trials are briefly described in table 1, and the main characteristics of some of the large-scale trials are shown in table 2.

The Institute's complement of clinical trials represents a balance between several factors. The trial must be in the NHLBI's purview, and its design and management must require the Institute's research expertise. There are some validation studies aimed at questions related solely to health service delivery (consequently not falling within the Institute's purview) but the NHLBI would probably act in an advisory capacity. Second, the clinical trial must satisfy requirements related to such factors as the scientific basis for the underlying

TABLE 1. NHLBI large-scale clinical trials

Currently, the National Heart, Lung, and Blood Institute is funding several large-scale collaborative studies. Eight of the large-scale trials currently under way or completed are briefly outlined here. Their statistical characteristics are listed in table 2. The abbreviations for each trial are used to identify the trial in table 2.

Coronary Drug Project (CDP)

The Coronary Drug Project (now completed) sought to determine whether drugs that reduce blood levels of cholesterol and triglyceride confer any protection against recurrent heart attacks or improve long-term survival among men who have previously experienced one or more acute heart attacks.

Hypertension and Detection Followup Program (HDFP)

This program will determine, in the general population, the extent to which mortality and morbidity associated with elevated blood pressure can be reduced by systematic antihypertensive drug management.

Multiple Risk Factor Intervention Trial (MRFIT)

This investigation will determine whether a preventive program directed at the reduction of serum cholesterol, reduction of blood pressure, and reduction or elimination of cigarette smoking among men (ages 35 to 57) will significantly reduce the incidence of myocardial infarction and death from coronary heart disease.

Coronary Primary Prevention Trial (CPPT)

The Coronary Primary Prevention Trial will determine whether reduction of cholesterol by combined drug and dietary therapy will significantly reduce the antecedent rate of heart attacks and cardiac deaths in a group of hypercholesterolemic, but otherwise asymptomatic, men (ages 35 to 59).

Aspirin Myocardial Infarction Study (AMIS)

This study will determine whether administration of aspirin to persons who have had at least one documented heart attack will result in a significant reduction in cardiovascular morbidity and mortality.

Coronary Artery Surgery Study (CASS)

The Coronary Artery Surgery Study will evaluate the efficacy of coronary artery bypass surgery and its potential therapeutic effect in reducing morbidity and mortality in coronary artery disease.

Neonatal Respiratory Distress Syndrome (RDS)

This study will determine the effect of corticosteroids, administered 24–72 hours before parturition, on the incidence of neonatal respiratory distress syndrome, and whether the therapy has any adverse short- or long-term (up to 36 months) effects on the infant. Second, the trial will determine whether the therapy has any adverse short-term effects on the mother and whether morbidity from neonatal respiratory distress syndrome as well as total and cause-specific mortality is different in groups of infants who received antenatal steroids and those that did not.

Clinical Study of Intermittent Positive Pressure Breathing (IPPB)

The objective of this clinical trial is to evaluate the efficacy of long-term intermittent positive pressure breathing treatment when used as an adjunct to the overall care of ambulatory patients with chronic obstructive pulmonary disease. This evaluation will compare the use of IPPB with that of a powered nebulizer.

TABLE 2. NHLBI major clinical trials

Trial	Date initiated	Recruitment completed	Intervention duration	Total duration	Number of clinics	Number screened	Number of subjects	Cost to date[1]	Projected total cost
CDP	1965	1969	5 yr	11 yr	53	NA	8,341	$42,380,945	$42,380,945
HDFP	1971	1974	5 yr	11 yr	14	158,000	10,940	52,231,656	73,731,656
MRFIT	1972	1976	6 yr	12 yr	20	366,000	12,500	61,631,609	118,713,609
CPPT	1973	1976	7 yr	12 yr	12	500,000	3,800	42,338,801	103,311,801
AMIS	1975	1976	3 yr	7 yr	30	60,000	4,500	9,589,366	19,245,366
CASS	1973	1979	5 yr	11 yr	16	NA	800[2]	7,896,602	23,396,602
RDS	1976	under way	48 hr (before birth)	4 yr	5	NA	600	1,888,378	4,114,000
IPPE	1976	under way	3 yr	5 yr	4	NA	1,000	169,655	6,170,000

[1] As of February 1978
[2] Projected

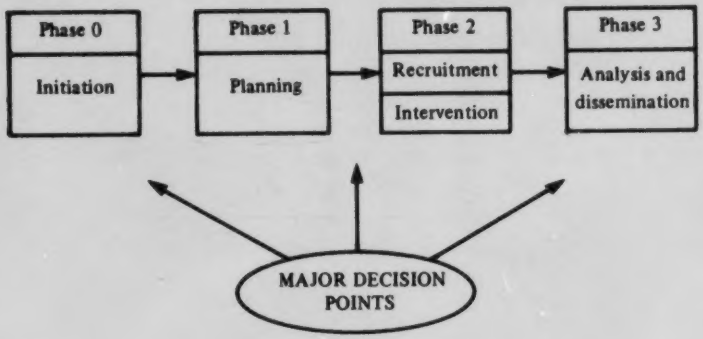

FIGURE 3. The clinical trial decision process

hypothesis and the potential impact of the trial. These factors have been incorporated into a clinical trial management process illustrated in figure 3. The process conceives of the trial as divided into four phases: initiation, planning, recruitment and intervention, and analysis and dissemination of the trial results. Separating each phase is a decision point at which the Institute either decides to commit funds to the clinical trial (the first two decision points), or to conclude the intervention portion of the trial (the last decision point).

The earliest phase of the clinical trial, initiation (phase 0), represents the genesis. Occurring largely outside the Institute, the trial's concept is first advanced, and skeletal trial designs are analyzed. This phase will be considered in detail later in this chapter. The final trial design and protocol are developed during phase 1, planning. The design process involves investigators from both outside and within the Institute.

Following the planning phase, the protocol is analyzed again to study feasibility and power, the current state of the science, and the potential cost effectiveness of the trial as a test of a public health regimen (see figure 3). After review by both outside experts and Institute staff, the NHLBI decides whether to commit resources to the trial itself. Phase 2, intervention and recruitment, represents the actual conduct of the trial. Beginning with recruitment of subjects, it blends into the intervention phase. The final decision point, whether to stop or continue the trial, must consider factors that are complex, both analytically and ethically. That decision rests ultimately with the Director of the NHLBI.

The trial then enters phase 3, in which results are analyzed and disseminated to the medical and lay publics. This process can involve consensus development, bringing together representatives of the health system to consider the implications of the trial: physicians, consumers, health planners, and third-party payers.

Initiating and Planning Clinical Trials

Large-scale clinical trials require extensive resources; their potential impact on medical practice and future research is enormous. Therefore, the decision to undertake one must be analytical and deliberate.

Initiating a clinical trial begins with discussions between Institute staff, biomedical scientists, and health care researchers on developments that could present significant potential for improvement of the Nation's health. In most cases, the trial is part of a logical progression of an idea as it emerges from basic science through clinical research to the point at which large-scale testing is required to determine the effectiveness and safety of treatment. Much of the Institute's work on trials involving atherosclerosis followed this path. The Multiple Risk Factor Intervention Trial, for example, is based on observations from several epidemiological studies, principally the Framingham Study,* that cholesterol, high blood pressure, and smoking are the three major risk factors for coronary artery disease.

The impetus for a trial, however, need not stem directly from basic and clinical research. The Coronary Artery Surgery Study (CASS), which is comparing the effectiveness of medical against surgical treatment for coronary artery disease, is motivated by the widespread and growing use of this intervention. Surgery is inherently more costly than medical therapy and may be justified, if the patient's clinical condition and longevity are sufficiently improved. This trial is the major test of the indications for coronary artery surgery, and its results should have a significant impact on the treatment of chronic coronary artery disease.

The initiation process culminates in a decision to devote sufficient Institute resources to design and plan the trial in detail. Full Institute resources will not be committed to the conduct of the trial, however, until after the design and final protocols are completed and reviewed. The decision to conduct the trial and the factors involved are discussed below. At this point, however, we turn just to the initiation process itself and the key factors involved in the Institute's decision to design and plan a clinical trial.

Proposals come to the Institute from various sources—from individual investigators and professional groups, from symposiums and workshops, from the Institute's advisory groups and Council and from the Institute's own staff. The information in the presentations derives from such sources as fundamental laboratory research, previous clinical studies, pilot or feasibility small-scale clinical trials, or related studies. A series of reviews follows: peer review, Institute Advisory Group review, Division review, Director's review, and the Institute's

*The Framingham Study is a 30-year epidemiological study of the residents of Framingham, Massachusetts, supported by the NHLBI.

Advisory Council review. Four key factors must be balanced before the Institute decides to devote resources to a trial: the state of the science; the feasibility of the proposed trial, including the likelihood of the results and the availability of the resources required; the potential impact of the trial on health care delivery and biomedical research; and ethical considerations. Even though resources are expended on planning, the Institute is not committed to conducting the full trial at this point. The major commitment of resources follows the planning phase and occurs only after a careful review of the trial design and its detailed protocol.

In deciding whether to initiate the planning phase of a trial, the Institute must consider other alternatives. For example, could other Federal agencies or the private sector support the trial wholly or in part? This avenue must be explored if only because NHLBI research funds are limited. Are alternative approaches to obtain the information desired from the clinical trial available? Is it possible, for example, to establish a registry to develop information on the effects of alternative treatments? After analyzing those results, sufficient data might be available to rule out the need for a clinical trial, or at least provide a better estimate of the parameters for such a trial. A registry does not require the extensive control of a clinical trial and often proves to be considerably less expensive.

Another facet of the decision is the timing of the trial. The time may be such that the state of the science is not stable, and rapidly changing concepts cannot underlie or buttress the trial; or it may be that a treatment is so widespread in practice that it is unlikely that medical practitioners would adopt the results of the trial. In such cases, the trial can be postponed or abandoned, or additional clinical research or a small pilot clinical study might be tried.

At the first decision point, these alternatives are weighed by the several review groups (figure 4) according to the four decision factors noted above. The decision to launch a trial weaves these factors together to test the feasibility of the study and to assess the resources required for the trial as a function of the potential impact of the trial. The first factor, the state of the science, represents the scientific basis for the trial; while the fourth, ethical consideration, dictates design constraints.

A clinical trial cannot be substituted for fundamental research; resources are much too limited for such luxury. The state of the science must be ready to buttress the results of the trial and to use those results for further exploration. A major consideration is the relationship of the state of the science to health practice. In general, there is a time window between development of a new treatment technique and its general adoption by the health community without validation. Once a treatment is adopted, it can be difficult to change practice, or the widespread adoption can make a clinical trial infeasible.

To launch a trial, the state of science must strike a balance between partial and complete a priori knowledge of the effectiveness of each treatment. If the zone of uncertainty surrounding treatment effects is too broad, a trial may

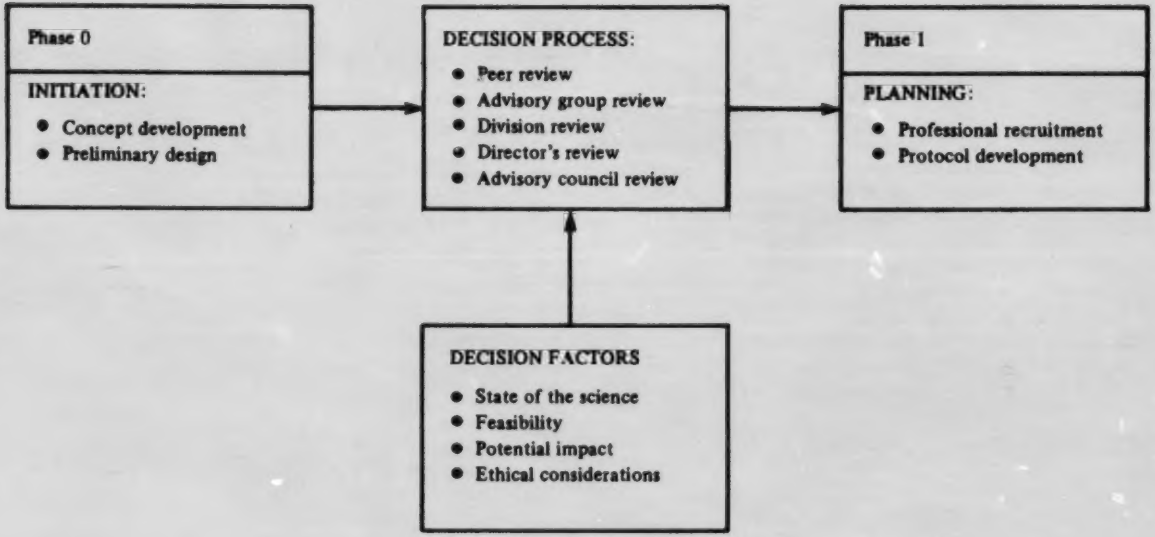

FIGURE 4. The clinical trial decision process: commitment to phase 1

simply be a substitution for more clinical or basic research. Alternatively, if much is already known on treatment effects, a clinical trial may have little, if any, chance of contributing any new knowledge, except to verify earlier studies. With such extensive resources required, a clinical trial must balance uncertainty about the effect of treatment and its safety with the readiness of the scientific and health care communities to accept and incorporate the results.

The feasibility of a trial reflects interrelated factors including the trial design parameters, the resources required for each design, and the desired results of the trial. The trial design framework includes the number of clinics and investigators, the number of experimental and treatment groups, the randomization process and stratification, and the type of blinding to be employed. These factors primarily affect the logistical feasibility of the trial and the scientific validity and generalizability of its results.

The design itself is based on a number of parameters that encode the state of the science and the potential results in simple analytic terms. The design procedure requires that the following be specified: the significance level (the maximum acceptable probability that the observed difference between the experimental and control groups is due solely to chance); power (the ability of the trial to detect differences between treatments); difference level (the magnitude of change desired between treatment and control groups); event rates (the frequency of occurrence of the primary response variable in the treated and control groups); the delay in treatment effect (the delay before achieving maximum effect after therapy); dropouts (the number of participants who will not follow the study protocol); and duration (the period of time to complete the study). The state of science is reflected in the estimate of event rates. The desired impact of the trial is reflected in the difference, significance, and power levels. Thus, assessing the feasibility of a trial is a skeletal design for that trial.

One important aspect of the feasibility study is the resources required for the trial. As shown in table 2, resources required for multicenter trials are quite extensive, and facilities and manpower are unfortunately quite finite. The number of clinics is limited, and the number of patients suitable for a clinical trial is not without end. For example, in the Multiple Risk Factor Intervention Trial, 1 in 70 of all males aged 35 to 59 in the United States was screened.

Cost, of course, is a key resource constraint. At a cost of $2,000 per patient per year for a cardiovascular clinical trial, increasing the duration of a trial or its sample size might increase its power, but it would also seriously increase the trial's cost. Financial limitations can make certain trials infeasible.

The well-designed, large-scale clinical trial has two major areas of impact: on health care delivery and on research. Impact on health care delivery in terms of prevention, diagnosis, and treatment of disease will result regardless of whether the trial result is positive (the hypothesis being tested is upheld) or negative. In the case of positive results, the trial will show that one treatment is more effective than another. If the trial results are negative, the inference to be drawn is

that there is little, if any, difference between the treatments. In the Institute's current trials, such positive and negative results are quite meaningful. For example, in the CASS, a negative result would imply that the surgical management of coronary artery disease is no more effective than the medical management of the problem. A positive result would show that one treatment is preferable in terms of mortality and morbidity outcomes.

The clinical trial has an exceedingly important role in health care delivery. Only a clinical trial can compare alternative health care treatments. In many cases, widely practiced treatments have not undergone a careful, controlled trial, although there may be consensus as to their effectiveness. Increasingly, health planners and the Congress are questioning the effectiveness of current practices. Therefore, there likely will be increased data collection, improved quality control, and, where warranted, larger numbers of clinical trials. But the effect of clinical trials on health care costs is a major consideration. The cost of the trial must be taken into account, balanced by potential savings in costs and possible improvements in mortality and morbidity rates.

Clinical trials also impact future research. Etiological or pathophysiological research seeks to relate intervention to outcome through an understanding of the mechanism of disease. In effect, the clinical trial steps back from the causal model and attempts to validate that model by relating impact on the disease process to output, that is, to relate therapy to the patient's response in terms of morbidity and mortality. Thus, the clinical trial bridges a gap from intervention to health outcome and can serve to open new areas of investigation. When clinical trials do not validate the underlying causal models, they can at once be the culmination of a research effort and the initiating event in a new research area.

Since the impact of the clinical trial is the "bottom line," costly, large-scale trials cannot be launched that will have minor or insignificant impact. To borrow terms from the economist, the benefits to be accrued from the clinical trial must outweigh the cost of that trial and at the same time must reflect a prudent use of the Institute's limited resources.

A discussion of costs and benefits alone in the decision to launch a clinical trial is not sufficient; ethical considerations must always be taken into account. Perhaps the primary ethical consideration is that patients must be fully aware of the evidence concerning the treatments under evaluation before enrolling in the trial. Patients and investigators alike must be convinced that no satisfactory evidence exists to differentiate the effectiveness of one treatment over the other under test, or over another treatment available outside the trial. Although this is a key ground rule, it also raises the dilemma of when to terminate the trial. As evidence accumulates during the trial, it is important to balance a set of factors relating to the possible spurious nature of the data and the expected treatment benefits against deleterious effects to be accrued by stopping a trial at too early a point. The welfare of generations to come must

be balanced with that of the patients in the trial. This dilemma will be dealt with in a later chapter.

Another ethical consideration is the assurance that sufficient testing has been performed a priori to ensure that the likelihood of toxic effects or side effects of therapies is minimized. It should be noted that, with the large numbers of patients randomized in some trials, toxic effects can appear that might not have been detected under smaller preliminary trials. The trial must be constantly monitored for such effects, and the trial protocol must have well-defined procedures for reporting and analyzing such effects.

Two Examples

The best way to illustrate the Institute's basis for initiating clinical trials is through example. Two such examples—one relating to a trial on mild hypertension and a second to a trial on the effectiveness of beta-adrenergic blocking drugs—are quite different, but they illustrate the decision analysis framework common to all Institute trials.

A Mild Hypertension Trial

A number of epidemiological studies as well as life insurance data have demonstrated that small increments in either systolic or diastolic blood pressure are related to an elevated risk of morbidity and mortality particularly associated with cardiovascular, cerebrovascular, and renovascular disease. From the "rice diet" of the 1940's to the step care regimen of today, there have been major advances in the control of high blood pressure. It is only recently, however, that proof is available of the effectiveness of treating patients with hypertension other than those with malignant hypertension. The landmark study of Dr. Edward Freis with the Veterans Administration Cooperative Study Group on Antihypertensive Agents showed conclusively the effectiveness of treating patients with diastolic blood pressures averaging 115 through 129 mm Hg. Succeeding studies have shown evidence of reduction in morbidity and mortality in patients with lower blood pressure; however, the toxic effect of long-term drug therapy has not been evaluated in the lesser degrees of hypertension.

By the early part of the 1970's, interest in the effectiveness of treating hypertension was widespread—in fact, worldwide. Studies were under way in Paris, London, the United States, Australia, and Sweden. In this country, three studies are of interest: the Hypertension Detection and Followup Program (HDFP) sponsored by the NHLBI, a study by the Veterans Administration, and a study in six U.S. Public Health Service hospitals. The HDFP study, still ongoing, is aimed at determining the effectiveness of a step care program as compared with regular care; i.e., simple referral of the hypertensive patient to his own physician; the Veterans Administration study was a 2-year feasibility study for a mild hypertension trial; and the goal of the Public Health Service

investigation was to determine whether a particular treatment of mild hypertension reduces the rate of development of degenerative vascular complications of the disease. In 1975 it became increasingly clear that, although the effectiveness of treating hypertensive patients with diastolic blood pressures greater than 110 mm Hg was receiving almost universal consensus,* the efficacy of treating approximately 20 million individuals with diastolic blood pressures between 90 and 104 mm Hg had not been demonstrated. There was increasing concern in the scientific community that it was important to determine this efficacy.

The importance was based on the following rationale. We may assume that some 20 million Americans had diastolic blood pressures in the 90-104-mm-Hg range and that at least 10 million of these persons persistently have a diastolic reading in that range. We also assume, based on survey data, that 5 million of these Americans are already under treatment with antihypertensive medication. If the treatment is, indeed, not effective, some 5 million people incur increased health care costs and drug side effects without any attendant benefits. However, if the treatment is determined to be effective, an additional 5 million or more hypertensives are not yet being protected from cardiovascular disease morbidity and mortality. The analysis is outlined in figure 5.

The growing interest in such a trial prompted the Institute to convene an ad hoc committee of eminent scientists to consider two questions: whether such a trial of mild hypertension treatment is necessary and feasible, and what the scope and basic design parameters for the trial should be. In other words, the committee was charged with determining the state of the science and the feasibility of such a clinical trial.

The committee met three times during 1976 and after intensive discussion and investigation of the issues recommended to the Institute that a full-scale study on mild hypertension not be done, despite acknowledging the importance of the subject. The committee felt that, to a degree, it was too late to do such a study because of the difficulties in keeping enough control patients active in the study (depriving some patients of treatment). Sentiments in the health care community already seemed strong and growing toward prudent treatment. (It should be noted that in the Hypertension Detection and Follow-up Program, both groups are under treatment.) Second, the cost was determined to be nearly $100 million, with a need for 10,000 patients enrolled for 6 years. That cost seemed to outweigh the potential benefits, particularly given feasible alternative actions in place of such a trial. Indeed, the committee recommended that ongoing studies on mild hypertension should be continued and supported.

*A consensus was to be formalized later and published in 1977 through the National High Blood Pressure Education Program [2].

			Potential trial results	
		Currently	Effectiveness demonstrated	Effectiveness not shown
Diastolic blood pressure between 90 and 110 mm-Hg	Number under treatment	5,000,000	10,000,000	0
	Number not under treatment	5,000,000	0	10,000,000
Labile hypertension	Number under treatment	0	2,000,000	0
	Number not under treatment	10,000,000	8,000,000	10,000,000

IMPACT	Decreased morbidity & mortality	Reduction in health care costs and side effects

FIGURE 5. Impact analysis of a mild hypertension trial

The report was accepted by the Institute and after review by the NHLBI Clinical Applications and Advisory Committee was presented through the director of the Division of Heart and Vascular Diseases to the Director of the Institute. On the basis of the recommendation, the NHLBI Director concurred with the Division director. It should be noted, however, that since that decision, the Institute has taken two steps to achieve the impact of a trial on mild hypertension: special grant programs in areas related to the etiology of hypertension, and the convening of an Institute Task Force on Hypertension to recommend research initiatives to the Institute.

In summary, the trial was considered in light of its potential benefits and the resources the Institute could marshal. At that time, due primarily to both ethical and resource considerations, it was felt that the trial was not warranted.

The Beta-Blocker Heart Attack Trial

Each year some 300,000 to 400,000 people die from sudden cardiovascular disease. Sudden cardiac death is believed to be due primarily to cardiac rhythm instability, possibly promoted by autonomic nervous system stimulation, and is widely recognized as a major public health problem. The inability to identify potential victims and the lack of effective therapies have posed major obstacles to solution of the problem. Recently, however, there have been significant advances toward understanding the mechanisms of lethal arrhythmias and, consequently, toward identifying subjects at risk. In fact, several European clinical trials of preventive drug therapy have yielded encouraging results, which prompted the Institute to convene an in-depth conference in May 1976 to consider the role of chronic antiarrhythmic drug therapy in the prevention of sudden cardiac death.

In discussing the magnitude of the problem, the conferees noted that 50 percent of the posthospital myocardial infarction deaths occur within 24 hours of the onset of new coronary symptomatology. They also noted that suspected arrhythmias account for 77 percent of these deaths and that pump failure accounts for only 23 percent. The risk of cardiac death is greatest in the early posthospital interval and progressively declines in exponential amounts after discharge. The conference noted that, because the majority of posthospital cardiac deaths occur in the first 4 months after discharge and are sudden, over 50 percent of the posthospital cardiac deaths following myocardial infarction are potentially preventable.

The conference also reviewed the previous research on antiarrhythmic drugs. Of particular importance was experience with several major clinical trials of antiadrenergic drug therapy, including studies of alprenolol and practolol (beta-adrenergic receptor blockers) in the prevention of sudden death in postmyocardial infarction patients. The conference found that the existing studies all had limitations: some too small to provide definitive conclusions, another testing a drug that was later removed from the market for untoward toxicity.

Trials of the two beta-blocker drugs yielded positive results, but it was felt that neither adequately answered the question as to whether long-term therapy with beta-blockers is beneficial in the secondary prevention of sudden cardiac death.

The conference participants were in agreement that a clinical trial of chronic antiarrhythmic drug therapy to prevent or delay the occurrence of sudden cardiac death was timely. The major conference recommendation was that the Institute pursue a broad program, including drug trials, but also seeking answers to basic questions on the mechanisms of lethal arrhythmias. Further recommendations were that the Institute attempt to gain further knowledge of the risk factors associated with sudden cardiac death, improve the identification of individuals at high risk, and provide for the possible emergence of more effective pharmacological agents through continuing investigation of electrophysiological action and the pharmacology of drugs still in an experimental phase.

The conference also offered guidelines for a clinical trial with respect to the population to be studied and the drug to be selected. Other general considerations were urged relating to certain pharmacologic principles, including utilization of drug dose-ranging techniques and the precise determination of the relationship between dose and blood level.

The recommendations from the conference were developed into a proposed design for a clinical trial, the Beta-Blocker Heart Attack Trial (BHAT): 4,000 postmyocardial infarction patients to be followed from 2 to 4 years. One-half of the patients were to be placed on propranolol, the remainder were to receive a placebo, and the major endpoint was to be death.

This proposal and its attendant justification were reviewed by two advisory committees of the Institute's Division of Heart and Vascular Diseases: the Cardiology Advisory Committee and the Clinical Applications and Prevention Advisory Committee. Both endorsed the project. The next step in the review sequence was to include the project in the Division's yearly implementation plan for proposed funding in the following fiscal year. At this stage the proposal was for a planning phase only for development of the protocol. The actual commitment to the full trial would await Institute analysis and review after completion of the protocol. This marks the second decision point shown in figure 3.

As a potential part of the Institute implementation plan, the proposal was reviewed by the Division of Heart and Vascular Diseases staff and by the Institute Director and his staff not only against the four decision factors but also in light of the Institute's current and future budgetary and program constraints. The large clinical trial, costing up to $25 million, meant long-term budgetary commitments that had to be balanced with needs in other areas. This trial's planning stage was endorsed by the Institute management.

The final step in the Institute decision process was a review by the NHLBI Advisory Council. The Council, appointed by the Secretary of the Department of Health, Education, and Welfare, represents both lay and scientific interests.

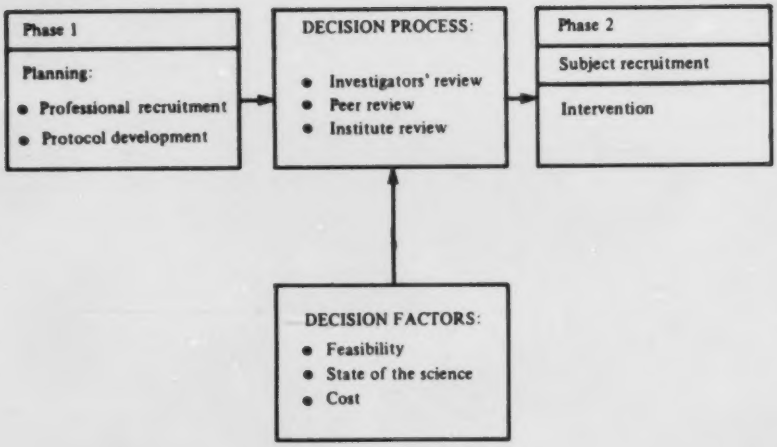

FIGURE 6. The clinical trial decision process: commitment to phase 2

The Council felt that the trial was an important effort and requested that the members be kept apprised of its progress. With the Council's approval, the Institute began the planning phase for the trial, which is now nearing conclusion. Scientists and Institute staff have developed the final protocol and the trial management and logistic structure. The next step in the trial is the second decision point in figure 3, a detailed Institute review of the protocol in light of the current state of science, the trial feasibility, and its potential impact (figure 6).

Conclusion

As health care costs continue to rise, the need grows concomitantly to ensure cost-effectiveness. A principal tool for such assurance will continue to be the clinical trial. However, the continued and projected scarcity of health care resources in general, and in particular for health care research, makes it vital that the process used for developing clinical trials be responsive to needs and responsible to fiscal constraints.

The NHLBI process focuses on a scientific or technical consensus in the decision to implement a trial. The technical consensus provided by Institute advisers is weighed against key decision factors in light of the Insitute's total program and its resources. The goal of the Institute is to make the trials maximally effective in their impact on research and on health care within fiscal realities and needs and the viability of the overall heart, lung, and blood research program.

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BASIS FOR INITIATING CLINICAL TRIALS

Duncan W. Vere

The United Kingdom has been, and remains, a satisfactory place in which to bring new drugs through clinical trials. However, there are increasing constraints on this process. There are presumed problems in obtaining volunteers, the time taken to pass regulatory hurdles, and factors that may bias the selection of new compounds for testing. Notable among these is the unpreparedness of many people from various walks of life to understand and accept risks from drugs and the rate-limiting "scarce resource" of man himself. Another important constraint is the sheer momentum of major drug companies. Evidence to substantiate these assumptions is hard to obtain; published material from the Committee on Safety of Medicines has been set alongside manufacturers' evidence in an attempt to gain evidence. A provisional conclusion from this is that the number of clinical trials made in the United Kingdom per new *product* is not declining if one allows for the median lag of 4 years from starting trials to product licensing. But in future, the reaction of many firms to regulation will be to get at least phase II of their clinical trials made outside the United Kingdom, a reaction that is a major issue.

There seem to be two main considerations about the reasons for starting clinical trials and the methods used to effect them. These aspects are:

1. What are the criteria for testing new treatments using orderly scientific methods, and
2. What are the criteria for selecting compounds for clinical trial?

This discussion will cover both these issues.

Issues imply debate, disagreement, or obstacles to progress. It has been said that, ideally, the objectives of the public, the medical professions, and the pharmaceutical industry should coincide. So let us look first at some idealized objectives for testing new treatments, and then consider how and why some issues arise.

The Secretariat of the Committee on Safety of Medicines kindly supplied much of the factual material quoted in this paper. The help of drug manufacturers that responded to the questionnaire is also gratefully acknowledged. Drs. T.B. Binns, Desmond Laurence, and John Griffin also contributed greatly by discussion and provision of source references, although the opinions expressed are the author's.

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Scientific and ethical objectives are inseparably intertwined. A bad experiment is unethical [1,2]. A set of idealized scientific objectives might be

1. To develop remedies against pathological processes, using scientifically valid methods.
2. To measure and minimize the risk of this to man.
3. To maximize the efficacy of drugs.
4. To measure and minimize the cost of these in terms of natural resources (raw materials, animals, human subjects, capital, time).
5. To advance knowledge.

A set of ethical objectives might be

1. To develop valuable new remedies to meet real human needs (the "medical mandate").
2. To use but conserve natural resources (the "natural mandate" to "have dominion over the earth").
3. To minimize harm to humans and animals.
4. To be profitable and provide employment.

In this paper the term "clinical trials" will be taken to include all stages from initial healthy volunteer studies through to some aspects of post-marketing studies (phases I to III, with some reference to phase IV).

What methods conform to these ideals, and what are the constraints that deviate them from their targets? First, the great majority of new remedies that come to trial in the United Kingdom are drugs that, at the time of trial, are still without a product license from the Committee on Safety of Medicines (CSM). Most trials are, therefore, of much smaller size than those described by Dr. Levy and have a different purpose. Also, the committee advises the British Licensing Authority, which issues two main kinds of certificate under the provisions of the Medicines Act of 1968. These are the clinical trials certificate and the new product license (for marketing). Both are required by law before any new remedy can be manufactured for sale. However, should an individual doctor wish to make his own clinical trial for a new therapeutic indication, he may do so by applying for an exemption from the clinical trial certificate stage. Many of the practical and ethical problems to be discussed center around the timing of various required tests around this basic procedure and applications for exemption therefrom.

In the United Kingdom, the Association of the British Pharmaceutical Industry (ABPI) has just laid down clear guidelines [3] for "good practice" in arranging clinical trials at every stage. The Committee on Safety of Medicines had issued briefer but related guidelines for those within its mandate, namely

phases II to IV [4]. The ABPI discusses both scientific and ethical aspects. In its *strict* authority the CSM can only discuss scientific and regulatory aspects. There are considerable differences of detail between the two papers [5-7]. But all trials should now be conducted under the Tokyo-Helsinki ethical rules [8], and it is understood in Britain that all clinical experiments, including trials, will be scrutinized by an independent ethical committee at the institution where the work is to be done. This includes trials carrying licensing certificates. There is an ethical anomaly here; the Government *requires* tests, but has no means to discuss or ensure their ethical quality, nor can it be called upon to defend its ethical stance save in the courts [9].

The ABPI guidelines assume that "each test compound or preparation has already been shown to possess properties which might reasonably lead to the development of an improved medicine for a significant human ailment," that there have been adequate prior animal experiments, and that the tests can be made under close medical surveillance. Details follow about the supervision of animals, the design of toxicology experiments in relation to the diseases to be treated, the biological properties of the drug, and the probable course of treatment.

An issue at once arises. ABPI guidelines, in defining the test substance, say that it shall be a defined entity, wherever possible, of the same quality as that intended for human use. But the CSM often asks that, at any stage of human testing, the substance tested should be the same as, or as close as possible to, the preparation to be marketed for patients. As Spink pointed out [10], this requirement adds greatly to the cost of early drug development. If during development an improved compound or formulation is discovered, the clock might have to go back to the start again, some patent life is lost, and a real conflict of advantage begins. The science and the ethics are impeccable, but the delay and cost might be lethal to a new compound and will certainly erode its profitability.

Finding the *pharmacodynamic* profile of a compound presents few problems, although we have run across some tiresome examples, such as compounds with parasympathomimetic activity causing cardiac arrhythmias in dogs, which are doubtfully relevant to man. It can be very difficult to know whether and how to proceed to human trials.

In the *acute toxicity tests* there has recently been public pressure to reduce the sacrifice of numerous animals. This led to an official examination of the LD_{50} procedure in the United Kingdom to see whether this was really needed, and a broadly based scientific committee decided that it was necessary. The ABPI guidelines detailed suggestions to follow for clinical toxicity tests, with stress on the need to relate these to the proposed human use of the compound. There has been a recent tendency to reduce the short-term chronic toxicity tests before single-dose volunteer studies in man (to 14 days for most drugs). This trend is compounded by a tendency to postpone the development of

plasma estimation methods for a new compound until after this stage. The reasons for these two developments are clear. People want to know as soon as possible whether a drug will work in man. This saves development costs and work. Also, as drug potencies rise and plasma levels fall, it becomes more difficult to provide assay methods at all. But it does mean that man is being exposed to drugs with less safeguard than before (i.e., both relevance and risk are increased). Should the drug *not* be found to be effective, there is no way to confirm that it was absorbed. This leads to a tiresome stalemate, reformulations, and delays, as an estimation method is hurriedly sought. This is another issue for debate.

The detailed reasons for bringing a compound to initial healthy volunteer studies have been listed by Burland [11] (table 1). When compounds are presented for clinical trial certificates, surprisingly it is often found that the plasma half time is unknown, or that isotope studies have been done with the label in a disadvantageous site in the molecule, or that in the toxicity tests animals were not dosed on every day in each week. The ABPI notes make appropriate recommendations to counter each of these defects.

From the start of the clinical trial program the Tokyo-Helsinki rules should be respected. But there are several obvious problems.

First, the British public cannot at present understand the concept of risk. This is scarcely surprising since even the Tokyo amendments [8] themselves state, in Part I, items 7 and 9, that the "hazards involved" in experiments with humans "are believed to be predictable" and that the subjects "must be adequately informed of the . . . potential hazards of the study . . . ." Since the tests are being made because the risks are believed in some measure to be *un*predictable and since the risk, even if quantitative or graded in the group, is always quantal (i.e., either present or absent) for the individual, it would seem a pity to inform potential subjects of the risks in those terms. In actual life, the less intelligent subject will usually respond to a statement about risks by a black-and-white decision: either "I'll have none of that," or "I'll leave that to you, doctor." In other words, he hasn't the apparatus needed to appreciate the significance of risk but translates it into luck or some other racecourse analog.

TABLE 1. Reasons for proceeding to initial healthy volunteer study

1. To find the metabolic pattern in man (to choose animal species for clinical toxicity tests).
2. To confirm pharmacological activity, dosage, and pharmacokinetic pattern in man.
3. To study formulations.
4. To study some interactions.
5. To satisfy regulatory authorities.

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To take this paradox a little further, we have had some character-building experiences that exemplify the problem. While shop stewards in some local industries eagerly recruit workers for initial healthy volunteer studies as an exercise in community benevolence (it has been necessary at times even to restrain their enthusiasm!), a group of faculty deans who were approached about student volunteers sent back a message that it was not their business to support the profit-making enterprise of the drug industry. Also, while some individuals are altruistic enough to volunteer for tests of drugs that may have potential value only for others, many people feel that they want their drugs only when they are ill. They want them pure, effective, and completely safe; but drugs must only be tested on other people. Yet those who clamor about the least evidence of drug hazard are prepared to smoke and drink and drive themselves to death in large numbers, while paying heavily for these privileges in hard cash. I have also explained elsewhere [12] how nearly impossible it is to obtain scientific estimates of the relative risks of adverse reactions to marketed drugs.

Members of regulatory authorities are permitted a largely negative attitude to risk. They are obliged to do one thing and one thing only: to stop drug development at the clinical trial stage if there is palpable risk. Their mandate is to regulate, but not to stimulate, drug development [13]. They, like the industry, can understand risk even if they do exhibit different attitudes toward it at times. In summary, I believe that we are in a position of great danger and difficulty about risks. All these pieces of evidence point in related ways to the view that different sections of the community have different abilities to understand and measure risks, and they strike partisan stances toward risk [14], be they volunteers or nonvolunteers, ethicists or scientists, or civil servants. But we cannot begin to handle the problems of drug development and regulation without sharing information about these risks. There can be no common goal, no participation of manufacturer, basic scientist, Government, and public until this nettle has been grasped and understood. Surely this is a major issue and needs a strong educational program to gain informed consensus before we can move forward to *stimulate* the development of necessary drugs, drugs that are as safe as they can reasonably be made to be [15-17]. The drug industry can state its view but cannot be responsible alone for public education; it would then be accused of being partisan by all other partisans. This must be a matter for national collaboration. Nor will it be possible, until this is done, to develop the risk-benefit analysis requested by Burrell [18].

Second, tests in standardized volunteers may not be representative. (This point was fully discussed by Azarnoff in 1972 and James in 1974 [19,20]). Recently we have found that healthy young male subjects recruited from certain local industries had raised serum enzyme levels before any tests were made. The cause was demonstrably alcohol, proved by history and improvement after withdrawal. One to two of every three subjects have shown this effect in isolated groups of volunteers. It has also become very clear how

necessary it is to supervise the subjects' journey home after tests, and to make it easy for medical help to be contacted thereafter. The ethical problem is that tests made to benefit A cause risk to B. They can only be made properly if B understands and accepts the risks and is protected from them as much as possible [1].

Third is the other set of issues concerning reproduction and carcinogenicity studies, when and how they should be made in relation to clinical tests. It is common practice to make these tests when they seem relevant [21]. If a drug is likely to be, or is related to, a weak carcinogen, if it is cytotoxic, or if there is a plausible link with carcinogenicity, such as a known endocrine mechanism, carcinogenicity tests are made before it is given to humans. With other drugs, usually those intended for prolonged use, tests are begun at the chronic toxicity stage and are aimed to be at least half completed before marketing. With some drugs the tests are never required. Similarly with reproduction studies, these are made before the drug is given to women, particularly when there is a plausible reason for doing them. But there are major snags. Carcinogenicity tests, and cheaper and quicker predictors that correlate with them, are at a stage of rapid development, so companies cannot anticipate the stance of a regulatory authority by reference to its past decisions. The definition of a carcinogen has been simplified recently by some agreement on what constitutes a neoplasm; the criterion of metastasis has gained growing acceptance. But this does not help with nonmetastasizing but dangerous growths such as hepatic adenomas, for which there are no agreed predictive tests. Nor does it ease the situation where there is evident animal carcinogenicity of doubtful relevance to man. With regard to the relatively new United Kingdom requirements for reproduction studies, it seems that many manufacturers regard them as imposing an unacceptable commercial burden, largely because of delay in passing phase II and consequent loss of patent life. But implicit in this argument is one that human beings are the only valid test species and that outside the United Kingdom the point has been discussed elsewhere [5,6].

Also we cannot find any regular way to release much-needed weak carcinogens for use in people who are over 60, or who are suffering from miserably disabling diseases, or who might only take them for short periods, because there is no way to balance the relative risks to them or to others who might take the drugs by accident. (Radio-iodine is an exception only because its administration can be so precisely controlled.) Meanwhile there may well be marketed drugs carrying "product licenses of right," which, were they innovated today, would never reach the market because they are animal carcinogens. One can only feel sorry for the manufacturer whose compound is a carcinogen for a large animal species, for the delays during testing, and the debate that follows will run into years. These problems are at present placing major obstacles before the development of progestogens and beta-adrenoceptor blocking drugs, but the problems are not light or easy to decide.

At the *clinical trial stage*, some major present issues are:

1. There are unresolved scientific problems in trial design. For example, diseases that come in clustered attacks (angina, epilepsy, migraine) are notoriously difficult trial subjects [22,23].
2. It has been said that "neither side knows what the other is doing" [24]. But industry at times expects, at times rejects, rigid guidelines [13].
3. Some clinical trials are such in name but not in essence. Many are now major surveys in general practice that appear to be thinly disguised promotion or market research. And in Britain, at present, general practice trials lack ethical supervision unless the doctors concerned actively request it.
4. There is debate about how many subjects should be treated for how long to establish the safety and efficacy of new drugs at this stage.
5. It is difficult to include women while ensuring that they do not become pregnant during the trial.
6. There is a marked lack of agreement about how reformulations, and particularly new drug combinations, should be tested. Manufacturers may assume that a mixture, on reformulation, will automatically take the same properties as its constituent drugs.
7. If bioavailability tests are taken seriously, there are marked shortages of volunteers for them, both subjects and investigators.
8. Although many checklists for clinical trial design have been prepared [25,26], few trials come up to these standards. It is not a part of the work of the British CSM to set standards for clinical trial design; it can only comment on lack of safety. Therefore, a marked variation in the quality of the trials submitted exists.
9. Frank discussion is needed on "medical blackmail" in recruiting volunteers, i.e., research made in the guise of care [2].

It has been shown that the early stage of human testing is determining the screening procedure for new compounds [27]. Strong reasons have been presented for the belief that our available scientific, educational, and ethical methods are poorly developed at this critical stage of the decision process about new drugs. It is therefore an urgent matter to improve these methods so valuable opportunities and resources are not lost in irrelevant effort.

We turn now to the second component of the mandate, the *selection* of new compounds. A prime issue here is that the National Health Service, though virtually the monopoly United Kingdom customer of the British drug industry,

has been unable to exert any major influence on the selection of new products for development. The aspect that relates to this chapter is that, although the Department of Health has clearly expressed views on product selection and promotion, it has been unwilling so far to support what we have called *economic* clinical trials: trials between alternative remedies that bring cost into the comparison alongside efficacy and other conventional decision points [28,29]. Be that as it may, it is noticeable that the Secretary of State has recently become the license holder for a few biological products and drugs against rare diseases that could not find a licensee in the pharmaceutical industry.

The participation of the general public in product selection, compared with that in clinical trial execution, has been minimal. This refers to organized outspoken interest, as for example by the Patients' Association and Community Health Councils, and concern with "internal pollution." (There has been much more public concern with drug adverse reactions.) But this is not to say that the British public has no influence on product selection. Public demand has a major but very general influence. People have become conditioned to "expect a drug" which might be unrelated to need. That need can also be, and is, manipulated by advertisements and propaganda. This is true of medical as well as "lay" opinion. The media and some consumer interests have at times adopted a largely "adversary" role, ignoring or grudgingly admitting drug benefits while amplifying exploitation if and when it is thought to occur. Sometimes they have been right; often they are wrong. But the times when they have been correct give strength to their growing voice. There is strong feeling in some places against animal tests and this becomes linked with ideas about "human guinea-pigs." The fact that the shrillest voices are often those of nonparticipants makes one feel that their views might be moderated by more participation in the actual process of new drug selection.

How do companies in fact select new drugs for development through the clinical trial stage, and what constraints work to distort the idealized process? The chief points have been reviewed elsewhere [30]. Companies vary in their methods; this author was privileged to attend a "think tank" conference devoted to new product selection by one company. There was a lot of wise discussion there about the practical and ethical aspects, and some definite proposals emerged from the large group. However, the participants were all drawn from industry, medicine, and relevant scientific fields. Should there have been representatives of the general public? Most firms probably use much smaller groups to advise them on such decisions.

Numerous constraints operate to divert the decision process from or into narrow areas within those ideal ethical and scientific objectives with which this chapter began. The industry is often blamed for a variety of ulterior attitudes, and sometimes the comment may be fair. But the inverse process is often overlooked: industry, like an expanding liquid, will take the shape of the container into which it is forced. Those who fashion the container must take

primary responsibility for its shape. To list only some of the more important constraints, one might mention resources and regulations, markets and motives.

Humans are a scarce resource, be they trial subjects, patients, or clinical pharmacologists [17]. So are the places where tests can be done, and they are curiously sporadic. Money has been discussed endlessly, particularly the fact that, in any research (R) and development (D) budget, more spent on D means less spent on R [31,10,32]. And costs are rising logarithmically [33,10]. These interact with the effects of regulation, which, of course, tends to divert costs upwards and from R to D. A more subtle problem is failure to allow for, and recruit, invisible savings from the National Health Service in R&D budgeting. If a drug undergoes costly development and succeeds as a remedy, there may be huge gains to the consumer. But the more the consumer saves, the less–in some situations–may return to the firm that made the development. A common assumption in developed nations is that new development depends on growth. But the drug industry seems to be completing its phase of logarithmic growth [34,16]; is it now to abandon new drug development? No-fault liability will also impose a new financial drain [2]. The balance of finance flow is sophisticated and can move either way. But it would be a foolish manufacturer who ignored that flow in the process of compound selection. Perhaps the scarcest resource is serendipity, but many important new drugs, and new drug effects, are discovered only by its use [14,17,35].

The problems of regulation are no less daunting. A drug may easily gain a clinical trial certificate in the United Kingdom when it is evident to those who grant it that the compound will never gain a product license. But it is not within the authority of the CSM to advise companies; it can only advise the licensing authority. There is ample room for misunderstanding.

Toxic drugs that might benefit groups immensely are turned down if those minorities cannot be sharply defined. There is also the "regulation within limits" effect. By this is meant if a regulation affects only one drug, or a small group of drugs, it will have little effect; whereas its impact may be devastating if it affects a major class of compounds forming a large fraction of the total output of an industry. For example, if one drug in a group of compounds is found to be a carcinogen, perhaps in one species only, blocking its progress will have a small impact on industry as a whole. But if a class of related drugs are under suspicion as carcinogens, the whole industry may be choked in relation to that large area of expertise and cost.

Curiously, industry pays highly for its confidentiality. This, of course, is widely misunderstood to be the brainchild of cutthroat competition, when in fact it is rendered essential by the patent laws [33]. But, if one company has a confidential suspect carcinogen on its development list, many others with related compounds may find the regulatory authority curiously obstructive toward them. It is alleged, one cannot say how truly, that the first thing the industry knew about possible carcinogenicity in one group of drugs was what

they read in the annual report of a regulatory agency. The problem is how to manage industry, and the impact of regulation on it, so it avoids both bureaucratic blight and an enterprise that exploits, and reaches the middle ground of fruitful fulfillment. This moral obligation is discussed by Binns [36], but it seems to be an obligation for the regulatory authorities as well as for the drug industry. The world waits interestedly to see the effects of the U.S. Food and Drug Administration's (FDA) new codes of good practice [37,13]. The weight of regulation soon shows diminishing returns in terms of safety assurance in relation to cost. It is not in the public interest to "idealize ourselves to a standstill" [31].

Markets are important constraints. With regard to clinical trials, it has been urged that they should not be repeated needlessly, though some repetition may be required to take account of racial, cultural, nutritional, and economic differences [38,14]. Unfortunately, some serious problems tend to be overlooked. Major nutritional differences can affect drug choice within a single community in Africa [39]. Wealth and prestige can also distort drug choices markedly in developing nations [40], and the industry would be wise not to amplify those instances. Differences in compliance also contribute to the distortion, as in the grotesque instance where coil contraceptives were being used as hair curlers by one group of African women. There are also striking differences in therapeutic preference [41]. Regulatory authorities and drug firms may, in such cases, reach different conclusions about risk-benefit assessments. Overregulation might drive firms to make trials in places where technical and ethical standards are less acceptable than they would have wished [42].

In an attempt to consider such arguments in relation to clinical trials in the United Kingdom, it is not difficult to obtain data about new product license and clinical trial certificate applications from the published reports of the CSM (figure 1). Its interest lies in the fact that the drug industry has long regarded the United Kingdom as a good place for clinical trials, where data can be generated to a high standard and sustained and stable clinical cooperation are possible. What is more, the number of new product license applications has fallen only slowly under the influence of recent industrial recession, so one might expect to see sustained numbers of clinical trial applications. Figure 2 suggests that this is not the case. The number of new clinical trial certificate applications fell significantly over the whole period under the voluntary (Committee on Safety of Drugs) period and on into the CSM period after 1972. It might be thought that this could be explained simply by the rising number of exemptions granted from formal clinical trial applications, i.e., to doctors, rather than to pharmaceutical companies (figure 3). But this is not so, as the ratio of clinical trial certificate to new product license applications shows (figure 3). The figure has two histograms representing the probable extremes of the lag between starting trials and applying for a product license. The number of clinical trials done in the United Kingdom per new *product* (i.e., *not* per new chemical entity) reaching the United Kingdom market seems to be falling

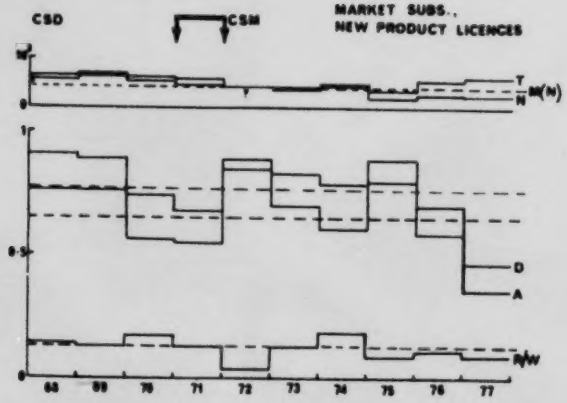

FIGURE 1. Histograms showing numbers of market submissions made to the Committee on Safety of Drugs (CSD) and product license applications made to the succeeding Committee on Safety of Medicines (CSM). T: total numbers; N: new submissions; M(N) mean of N. D is the proportion of T decided, A those approved, and R/W those rejected or withdrawn by years, with their means (broken lines). The arrows show the period of CSD - CSM transition. [*Source:* Annual reports of U.K. Committee on Safety of Medicines.]

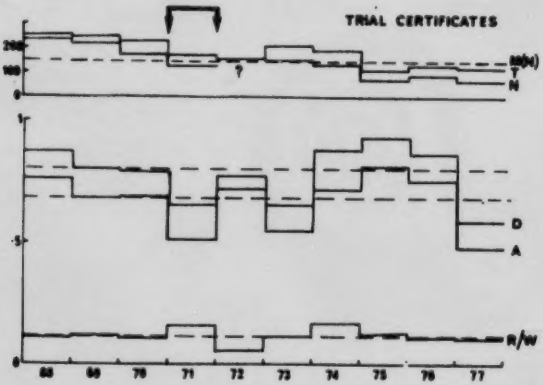

FIGURE 2. Histograms showing numbers of clinical trial certificate applications on the same ordinates as figure 1. T: total; N: new; and M(N), mean of N applications, by year. D is the proportion of T decided, A those approved, R/W those rejected or withdrawn, with their means (broken lines). [*Source:* reports of Committee on Safety of Medicines.]

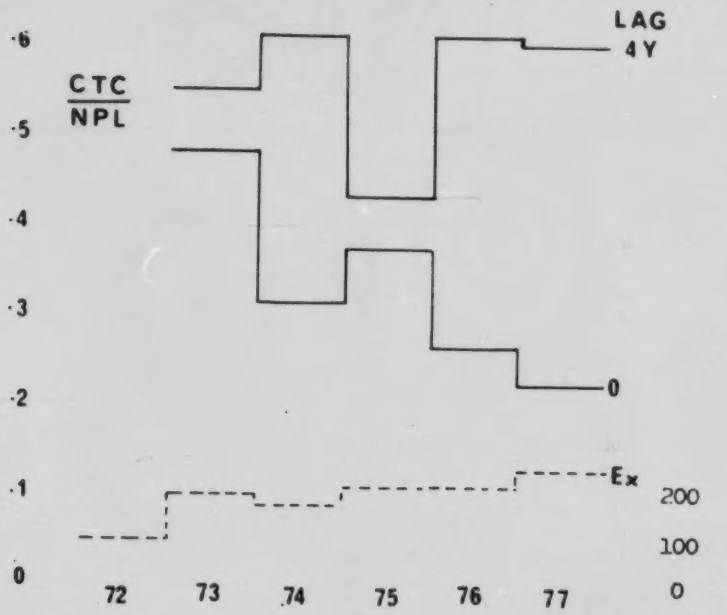

FIGURE 3. Numbers of exemptions (Ex) from clinical trial certificates requested by doctors each year (broken histogram). Ratio of clinical trial certificate applications (CTC) to new product licenses (NPL) by years (solid lines), assuming a lag between CTC and NPL of 4 years (upper histogram) and zero (lower histogram).

if one fails to take account of the lag between the start of trials and marketing. This development period varies markedly (for example, it is much shorter for antibacterial drugs and may then be as brief as 6 months). It is, therefore, dangerous to generalize from such rough data as those in figure 3. It would be necessary to trace the history of each product separately to be sure, although the truth presumably lies somewhere between the top (4-year lag) and bottom (zero lag) histograms in the figure. These figures point to two new features that cannot fail to cause concern. The steady rise in applications for exemption may well reflect attempts to "beat the system." (Three examples of this are known to this author.) And the even more brisk increase in those product license applications stalled "whilst awaiting information from the applicants," may represent a growing control over details by the regulatory authority.

In an attempt to carry the argument further, a questionnaire was sent to 54 manufacturers, who had among them 92 products listed as new introductions. In the United Kingdom this means that these products had been marketed within the last 4 years. Each manufacturer was asked to state, for each product, whether he had or had not experienced difficulty in obtaining clinical trial facilities in the United Kingdom. Also if the firm had gone overseas for the

clinical trials, why was this done? Table 2 shows the results of the survey to the time of writing.

TABLE 2. Number of products recently introduced into the U.K. market

	U.K. Origin	Other
Number of products	11	39
Initial healthy volunteer study (IHVS)	16	33
Clinical trial (CT)	43	7
	Median	Range
Time from beginning any clinical trials to product license application (years)	4	.25-12
	Yes	No
Difficulty in making trials		
IHVS	0	18
CT	3	25
Difficulty in obtaining volunteers in United Kingdom		
for IHVS	7	18
for CT	8	24
as clinical investigators	10	24
Ethical Committee's services obtained	26	13
Repetitive trials made in more than one country	44	3

Source: Questionnaire sent to 54 drug manufacturers.

It can be concluded provisionally, therefore, that people do not seem to be experiencing difficulty in mounting clinical trials in the United Kingdom. The fall in trial numbers seems to be presaging a general fall in new product development, the reasons for which are beyond the scope of this paper.

The main complaints of manufacturers' representatives were of difficulty in bringing the time of initial healthy volunteer studies and clinical trials forward (partly because of the reproduction studies), difficulty in finding clinical investigators for necessary but uninteresting drugs, and the annoyance of investigators who must complete the paperwork in the United Kingdom. They admit that these factors are taking some studies abroad, but not to situations they would deem to be inadequate on scientific or ethical grounds. Both of these contentions are debatable.

The last set of constraints on clinical trials to which I will refer is concerned with motives. Here it is impossible to be concrete or quantitative but it is obviously true, and several manufacturers and investigators have readily agreed in private conversation or in print[30,34], that the momentum of a company is a major determinant of decisions about clinical trials. The sheer size of the firm, and of its research units, and its degree of commercial domination in a given market are all "critical mass" factors in making such decisions. In one sense, although a firm's growth makes new opportunities possible, its sheer mass and forward direction can be inimical to change.

A need for attention to motives is clear. How to do it is not so clear. When a set of cogs is moving it is often hard to see which is the driver (figure 4). Proper

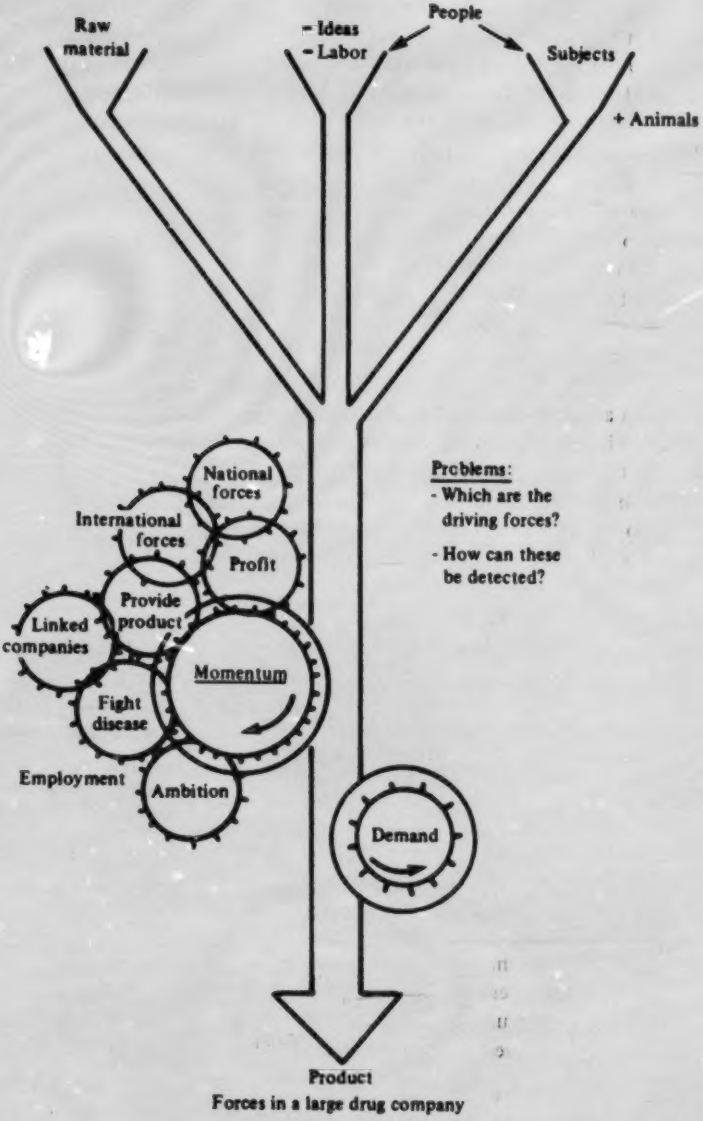

FIGURE 4. Some of the forces operating in a large drug company. It is impossible to identify which cog is the main driver, or which are accelerating and which retarding onward movement, or which may be sustained substantially by momentum.

clinical trials can only be made when clinical need is the primary driving force. The author has seen several studies made in developed countries where unsuspecting, poorly educated patients had participated in a piece of pure research, not without hazards, in the belief that it was their ordinary medical treatment. There is a relevant discussion of this point by Blackwell [42]. A postgraduate student from a developing nation, on successfully completing his course in clinical trial methods, told me that all he had learned was of little use. There were not, he said, enough honest colleagues within reach of his workplace to enable him to mount clinical trials with such designs. So ethical committees are essential, not only for their primary purpose but also because, in the long run, dishonesty is highly inimical to all clinical trial work.

The major issues in selecting products for clinical trials in the United Kingdom seem to be

1. What are the scarce resources? Often they are human [44].
2. What is sufficient clinical testing?
3. What are the external constraints—patent life, markets, human needs [45]?
4. Who should make the trials, and who should pay for them to be made? Should it be industry, the National Health Service, academic departments, or all these?
5. What is the driving force for development? Is it "momentum," money, ambition, human need, or a combination of these [46]?

The "long shadow of thalidomide" [16] has shaped our present policies toward clinical trials and drug regulation. But we should be as wary of mindless momentum here as everywhere else. The questions that now come to mind are these:

1. Was the thalidomide experience characteristic, or typical, of severe drug disasters that might befall us?
2. Does thalidomide have predictive value for all possible adverse drug reactions?
3. Could another thalidomide-sized problem be detected and prevented by our present systems?
4. Does the public understand the nature of the risks which it aims to avoid by its present regulations?

If, as seems to be the case, the answer to each of these questions is a qualified "no," it would seem sensible to explore alternative ways of regulating the human trial stages of new drug development. Fear of a fearsome hazard and the desire to be seen to have done something to avoid it are poor alternatives to logic when it comes to working out these trials.

Fear is a fair motivating force, but a poor guide. The prime ethical issues are what risks should people be invited to accept, knowingly or unknowingly; who

should be asked to accept them; and how much should the tempo of new drug development be restrained to minimize these risks effectively. Life would be more fair if a battery of optimal preclinical tests could be agreed internationally, applied equally in all countries, and the patent life of products adjusted in some agreed way to permit legitimate and necessary returns from investment. This can only come about if everyone is willing to participate in the process of developing new treatments through clinical trials, guided more by scientific and ethical knowledge than by adversary pressures.

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DISCUSSION

Edward J. Sondik

The stimulating papers by Dr. Levy and Dr. Vere on the basis for initiating clinical trials approached the topic differently. Dr. Vere concentrated on drug trials, while Dr. Levy used two clinical trials to illustrate the general process and procedures used in decision-making at the National Heart, Lung, and Blood Institute. The papers raised a variety of questions ranging from the constraints and regulations imposed on practitioners in the United Kingdom participating in clinical trials to the role of the National Health Service in clinical trials. Also discussed was the cost of clinical trials, stressing the difference in scope between trials in the United States and trials in the United Kingdom.

In his remarks, Dr. Vere mentioned exemptions for practitioners in launching clinical trials. Responding to a question on such exemptions, he noted that practitioners in the United Kingdom follow different regulations and procedures in launching a trial than does a drug company. He also noted that at times it may not be clear who actually initiated a trial, and, therefore, it will be unclear as to what process should be followed. Dr. Vere stressed institutional review committees and their role in ethical oversight and approval.

In response to a question on the low number of clinical trial approvals, Dr. Vere mentioned, as he had during his presentation, that many applications remain in "limbo" before the CSM and that these applications await only minor details from the drug company. The reasons why these applications are not expedited are not clear.

The disparity in cost of European and American clinical trials was raised. The $100 million cost for the proposed, but rejected, mild hypertension trial consisted of about 70 percent personnel costs, which seems to consist of about the same proportion in both Europe and the United States. It was pointed out that costs for trials in the United States include items that may be covered by the British National Health Service, including clinic facilities, costs of seeing patients, and drugs.

Of particular interest was a discussion of the role of and potential for the trial to find and evaluate drug side effects. It was noted that large trials with more patients watched over longer time periods have this benefit; the question of whether the trials should be designed to identify side effects of a particular incidence was raised but not resolved. The usefulness of clinical trials for testing purposes beyond determining drug efficacy was also discussed with general approval. Dr. Levy noted that many of the NHLBI trials fall into this category of testing nondrug preventive or therapeutic regimens.

Questions were also raised as to how independence of funding and scientific integrity are maintained in the United Kingdom. Dr. Vere noted that this independence is most difficult to maintain for trials of therapies or drugs that have

been on the market for some time. He feels that the National Health Service has an important role in this area, particularly for trials related to cost comparisons. For other trials, Dr. Vere noted that in the United Kingdom his group serves as a liaison between investigators and industry and through their counsel and thereby tries to effect the independence of funding and scientific integrity. However, Dr. Vere's group activities are confined to a local area, and he is not familiar with practices elsewhere.

Part 2

RANDOMIZED CONTROLLED TRIALS IN HEALTH SERVICES RESEARCH

T. W. Meade

Worldwide escalation in demands for health services has prompted an increasingly critical attitude toward the effectiveness of nonpharmacological and pharmacological treatments. There is a growing place for randomized controlled trials in health services research on topics such as place of treatment, length of stay in hospital following surgery, the effectiveness of remedial therapy in chronic disease, and the value of prescriptive screening. Trials of this kind have their own inherent difficulties, but one can look to the methods developed in drug trials for general guidance on design and analysis. Careful initial choice of topic is an essential prerequisite for ensuring that a trial is likely to be of practical value. Multicenter studies are often necessary if adequate numbers of trial participants are to be achieved. Universally applicable and valid measures of outcome for use in trials where "quality of life" is the main concern are not yet available, and individual trials will often have to derive and validate their own measures. Most health services trials cannot be double- or even single-blind, and special steps usually have to be taken to avoid the strong consequent possibility of biased measurements. For successfully completed trials, there still remains the question of whether, and if so how, their results are implemented.

Much of this symposium is concerned with the large and ever-growing body of experience with clinical trials of pharmacological methods of treatment or prophylaxis. A great deal of current clinical practice, however, consists (as it always has) of management by nonpharmacological means. This chapter considers the value, development, and problems of randomized controlled trials of various aspects of health care besides those to do with the efficacy and safety of medicines.

A major stimulus to trials of the sort to be discussed has been the worldwide escalation in demand for health services, and the costs of these services. These factors have prompted increasingly critical attitudes toward traditional treatment methods that are often unsupported by firm evidence. This seems especially true of labor-intensive services, such as various types of remedial therapy and, more recently, coronary care. In the case of minor surgical procedures, several studies on length of stay in hospital have been carried out, and attempts have been made to see whether some can be performed with equal effectiveness and safety on an outpatient basis. A good example of such a trial was the

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comparison of inpatient treatment of varicose veins by stripping with outpatient injection/compression sclerotherapy. The two methods were equally effective clinically, but patients preferred the outpatient treatment, which was also considerably cheaper to them and the health service [1,2]. (A recently published followup study of patients in this trial [3] has, however, shown that those treated by stripping required significantly less treatment during the ensuing 5 years than those treated as outpatients; it is clearly important to consider both long- and short-term implications.) The rapid development in the last few years of methods with potential application in the field of prescriptive screening for early diagnosis and treatment is another factor stimulating clinical trials in the health services research field.

Underlying all these more or less specific areas of concern is the general problem of resource allocation. This chapter makes no attempt to suggest how this should be resolved within any particular health care system; it is concerned only with the randomized controlled trial as the means of establishing some of the information needed to decide what services should be provided, and how.

Controlled Trials in Health Services Research

There is no reason why controlled trials in health services research should not be approached in basically the same way as drug trials. The extent to which it may be necessary to depart from some of the basic rules for drug trials is one measure of the difficulties of using the randomized controlled trial for other purposes, and also of the degree to which there will be reservations about the results obtained. Based on the experiences of some health services trials that have been carried out, or are in progress (all within the framework of the National Health Service), table 1 summarizes the main issues to be considered.

Why Randomize?

It is still surprising how many clinicians and administrators are prepared to accept comparisons based on nonrandom allocation of treatment in circumstances where it is clearly inappropriate to do so. It is true of a number of

TABLE 1. Randomized controlled trials in health services research

1. Why randomize?
2. Choice of topic
3. Who should do them?
4. Trial design
5. Numbers
6. Measures of outcome
7. Blindness–policy on results
8. Implementation of results

conditions treated in hospitals in the United Kingdom, for example, that case-fatality in teaching hospitals is lower than in nonteaching hospitals; table 2 summarizes some of the comparisons made by Morris [4]. These data have sometimes been interpreted as showing that standards of care are higher in teaching than nonteaching hospitals. This may or may not be true, but it is equally likely that the characteristics of the patients admitted to the two types of hospital, rather than the quality of treatment received, were responsible for the differences in outcome. The former explanation was, indeed, shown to account for much of the difference in case-fatality following admission for hyperplasia of the prostate [5], since 78 percent of admissions to nonteaching hospitals were emergency admissions, compared with only 22 percent of those to teaching hospitals. A partial solution to assessing outcome in the majority of instances where data based on random allocation to treatment are not available is to match patients for personal, medical, and social factors thought to be relevant and then compare outcome. This approach has its own theoretical and practical difficulties, however, and can result only in matching for variables on which there are data. Characteristics that have not been specified, or cannot be measured, may still be unequally distributed between the two groups, which makes valid comparisons difficult or impossible. Under ideal conditions, randomization establishes two or more groups that are, as groups, not merely similar but identical (at least within narrow limits) not only in terms of features that can be specified and measured, but also in terms of those that cannot. On the numerous occasions where random allocation is not possible for practical or ethical reasons, cautious interpretations of comparisons based on other types of data have to be made. But it is clear that the comparison in which the greatest confidence can usually be placed is that resulting from random allocation to treatment (type, place, length, etc.).

TABLE 2. Case-fatality in teaching (TH) and regional board (RBH) hospitals (England and Wales 1967-70)

	Case fatality (%)	
	TH	RBH
Hyperplasia of prostate	1.6	3.1
Myocardial infarction (men)	13.5	17.3
Chronic bronchitis (men)	9.9	14.7
Appendicitis	None	0.08
Peptic ulcer (men)	1.7	2.5
Diabetes	2.6	5.2

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Choice of Topic

In his 1971 Rock Carling lecture, Professor A.L. Cochrane [6], a leading exponent of the randomized controlled trial in the health services as well as the biomedical field, set out a wide range of topics amenable to study by these trials. "You should randomize until it hurts," Cochrane said, although even he acknowledged that the randomized controlled trial is not the only way of assessing effectiveness.

Vital statistical data [7] and comparisons derived from studies based on matching rather than randomization can be of value in assessing effectiveness. In addition, we should not overlook experience and intuition as a basis for decision-making. It is clearly not possible to study every facet of health care whose value is still uncertain using randomized controlled trials, or even by other research methods. A major part of the skill in undertaking controlled trials, therefore, undoubtedly lies in deciding which topics to study. Research teams capable of conducting trials to reasonable standards are still relatively scarce and should usually be expected to undertake them only if it is likely that the findings will influence decisions still to be made, or clinical practice that can be altered. There is limited value in even the most elegant trial if nothing happens as a result of it, particularly if the likelihood of its making no impact can be anticipated. As far as the United Kingdom is concerned, it is hard to think of cervical carcinoma screening being discontinued, or even reduced much, on the basis of a randomized trial that showed that it was ineffective in reducing mortality. (By the same token, given the conviction among many medical professions and most of the lay public that this type of screening is effective, and some observational data supporting this view [8], such a trial could in any case hardly be carried out now.) In the case of screening for breast cancer, considerations of cost and organization led to the decision in the United Kingdom not to repeat the Health Insurance Plan's study [9] of the worth of mammography, even though it is clear that it would be valuable to see its findings either confirmed or refuted. The benefit was not considered large, and it appeared to be confined to older women. Instead, studies are now being planned, or are under way, to examine organizational implications of a screening service. These will include comparisons of mortality according to type of screening procedure, but the latter will not have been allocated at random.

Ethical considerations are, of course, crucial in selecting topics for controlled trials, and the issues are not always as cut and dried as might be supposed. In the area of inborn errors of metabolism, for example, it is argued by some that withholding treatment that may possibly be effective cannot be justified under any circumstances; others argue that the treatment may be unpleasant as well as perhaps being ineffective and that an unequivocal answer is needed in the interests of future patients. This is still an unresolved controversy, even in the case of the dietary management of phenylketonuria. The

ethical question clearly has to be decided on its merits in each particular case. For purely practical reasons, if for no other, it is unwise to start a controlled trial where the clinicians concerned may, under pressure from others, have given only grudging approval on ethical grounds. This is an unsatisfactory situation from everyone's point of view and can lead to frequent departures from the trial's protocol and a great deal of wasted effort.

Who Should Do the Trial?

Epidemiologists sometimes tend to think they can do better clinical trials when they are left to their own devices, involved only passively—not actively collaborating with a clinician who provides patients. Most trials should involve epidemiologists or statisticians, but it is usually desirable that the day-to-day conduct of a trial of remedial therapy, for example, should be primarily in the hands of clinicians and therapists providing the service. The results of a trial carried out under all the difficulties of a routine service department may be less polished than under ideal conditions in terms of the circumscribed objectives of the trial, but they are likely to be more acceptable to others providing similar service elsewhere. Not only does the close involvement of the clinician from the outset mean that the trial will be carried out under real-life conditions, but special care can also be taken to see that the precise aim of the trial is specified in meaningful terms. Indeed, the initiative for trials should increasingly come from the clinicians for this very reason, the epidemiologist and statistician providing advice on trial design and analysis. An example of a trial that evolved in this way is that of Simpson et al. [10] on "right" stay surgery. There have been several trials showing that postoperative inpatient stay can often safely be shorter than the conventional time. In these, however, the "short" stay period has usually been the same, within narrow limits, for all the patients to whom it has been allocated. Simpson et al. [10] considered that there is unlikely to be a single duration of postoperative stay that is optimal for all patients. Their randomized trial therefore compared the effects of discharge from hospital at a "fixed" postoperative interval of 10 days with discharge when certain clinical criteria considered appropriate for the two operations concerned (cholecystectomy, vagotomy) had been fulfilled; i.e., "right" stay. Table 3 summarizes the criteria used, and table 4 shows the distribution of postoperative stays in the two groups. It is clear that there is indeed a range of "right" postoperative hospital stay intervals, but the mean was actually less than the "fixed" interval, itself short by comparison with many other surgical units. Clinical outcome in the two groups was similar.

Trial Design

The design of health services trials should be approached in the same way as drug trials as far as estimating required numbers, the need for stratification,

TABLE 3. Criteria for discharge after "right" stay following cholecystectomy or vagotomy

1. No intravenous infusion
2. No nasogastric tube
3. No intramuscular analgesics
4. Temperature less than 37.5°C for 48 hours
5. No help needed with washing, dressing, and eating
6. Taking fluids freely by mouth
7. Good appetite
8. Healthy wound
9. Healthy drain site
10. Normal bowel action
11. Normal micturition
12. No chest complications
13. Less than six analgesic tablets daily
14. Leukocyte count less than 10,000/mm^3
15. Hemoglobin at least 10 g/dl
16. Normal liver function tests

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TABLE 4. Distribution of lengths of postoperative stay following cholecystectomy or vagotomy

Stay (in days)	5	6	7	8	9	10	11	12	13	14
No. in "right" stay group	11	8	12	5	8	2	2	2	2	1
No. in "fixed" stay group			1		16	26	3		1	
Mean for "right" stay:									7.6 days	
Mean for "fixed" stay:									9.7 days	

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decisions between fixed sample designs and sequential analyses, and related aspects are concerned. Some of the practical difficulties that may arise are considered in more detail later. A frequent temptation one must avoid is to collect more information than is actually needed. The purpose of a clinical trial is to compare treatments; it should not be, although it frequently becomes, an excuse for collecting quantities of information to help predict outcome. Unless there is good prior reason to believe that additional information will contribute in this way, either by suggesting the need for a stratification procedure in the random allocation to treatment or at the stage of analysis, it is usually better left out. "Fishing expeditions" distract attention from the collection of high-quality data on those factors that are essential to the trial.

Unless the design of a trial such as that on stroke rehabilitation (see next section) is elaborate, it cannot give information about which components of the total treatment regimen are, or are not, effective. A process such as rehabilitation consists of both specific and nonspecific components. It may be that the general "tender loving care" associated with the delivery of a particular type of physiotherapy is equally or more effective when compared with the treatment itself. This sort of consideration has important implications for trial design and the selection of appropriate control circumstances.

Numbers

Statistical considerations will indicate the number of patients needed to detect differences of a given magnitude with given levels of confidence. Achieving adequate numbers is, however, one of the chief difficulties of health service trials; and a related problem is whether those who are eventually recruited are sufficiently representative to allow generalizations to be made from the results.

Table 5 details the availability of patients for a randomized controlled trial of different intensities of outpatient rehabilitation following a stroke, based on the experience of a district general hospital in London. Of the 704 patients with a confirmed stroke admitted between 1972 and 1976, a large proportion (35 percent) died within 2 months, mostly while still in hospital. A further 16 percent had made a full recovery soon after admission or discharge. About 28 percent had either been dependent on others prior to the stroke or had other conditions making it impossible for them to be considered for active rehabilitation. The 9 percent who had to be excluded because they lived outside the hospital's catchment area should also not be overlooked. The difficulty faced by the ambulance service in transporting patients across catchment area boundaries is a good example of the kind of apparently trivial but nevertheless real problems that have to be dealt with in the day-to-day conduct of trials. As

TABLE 5. Availability of stroke patients for trial of different intensities of outpatient rehabilitation, 1972-76

	No.	Percent
Died (within 2 months of admission)	243	35
Full recovery (soon after admission)	112	16
Other serious illness		
Previously dependent	196	28
Too old or frail		
Living outside area	61	9
Other reasons for nonavailability	9	1
Admitted to trial	83	12
Total	704	101

Source: Smith and Meade [16].

a result of these exclusions, only 12 percent or so of stroke patients coming to the hospital were eligible for inclusion in the trial. (Agreement to participate was almost total among eligible patients.) That percentage was in itself something of a surprise, apart from posing obvious practical recruitment difficulties. However, the reasons for exclusion from the trial are not very different from those that are used in ordinary district general hospital practice, and it may therefore be that despite the small proportion of all stroke patients entered into the trial, its results will nevertheless have some general applicability (provided the eventual number of patients who are entered is adequate). The population-based study of Weddell [11] on the outcome of stroke patients suggests that the low proportion of those available for the randomized trial is likely to be a realistic guide to the need for rehabilitation in this condition.

In another particularly well-known trial in the United Kingdom, the converse situation has arisen—adequate numbers, but doubts as to whether those recruited are sufficiently representative for general conclusions to be drawn. Mather et al. [12] recruited 1,895 men into a trial of place of treatment following myocardial infarction. After allowing for 457 patients for whom hospital treatment was mandatory, it was possible to allocate place of treatment at random in 31 percent of the remaining 1,438; home care was given to 226, and hospital care to 224. The 69 percent not randomly allocated were those whose care at home (151 patients) or in hospital (837) was decided electively—i.e., the general practitioner felt for a variety of reasons that randomization was inappropriate. Table 6 summarizes the overall results; there was no significant difference in mortality during a followup period of about a year, with the results favoring home treatment, if anything. Table 7, however, shows that in patients aged 60 and over, and without hypotension when first examined, results significantly favored home treatment.

The main controversy over this trial—or at least following its first report [13]—concerned two related points. First, it was argued that the high proportion of deaths that take place within a very short time of myocardial infarction meant that the trial was not in a strong position to assess the value of early

TABLE 6. Mortality after 1 year (approximately) by place of care following myocardial infarction

	Deaths	
	No.	Percent
Random home: 220	44	20
Random hospital: 218	58	27

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TABLE 7. Mortality after 1 year (approximately) by place of care following myocardial infarction in patients aged or over, and without initial hypotension

	Deaths	
	No.	Percent
Random home: 86	15	17
Random hospital: 101	32	32
$P < 0.05$		

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hospital treatment. However, analysis of the results by interval, from onset until the first receipt of medical care, did not suggest any superiority of hospital over home treatment (if anything, the reverse). Second, it has been claimed that since place of treatment was randomly allocated in only 31 percent of the patients originally considered for the trial, it is not possible to generalize about place of treatment. It is hard, however, to accept that this sort of criticism vitiates the results of the trial. It seems reasonable to conclude that in those patients who survive long enough for there to be a genuine choice as to place of treatment, care at home is at least no worse than care in hospital, and for some it may even be better. This trial has been particularly valuable in showing that basic questions can be approached ethically through randomized trials, and that these trials are feasible.

The need for adequate numbers in future trials means that those concerned with their financial support and organization will increasingly have to adapt the multicenter approach, so successfully used in drug trials by the Medical Research Council in the United Kingdom and the National Institutes of Health in the United States, to the needs and difficulties of health services studies. A particular concern arising from the involvement of several centers is likely to be the standardization of different treatment regimens between the centers, from qualitative and quantitative points of view. It is hard enough to ensure that participants in a drug trial receive and take their medication in accordance with the trial protocol. When it is a question of delivering a specified amount of physiotherapy, for example, the problems are in many respects even greater, not the least because more people are involved in the treatment transaction.

Measures of Outcome

In trials such as that on place of treatment after myocardial infarction [12], "hard" endpoints such as death, which is easy to ascertain and record, are obviously appropriate. In many health services trials, however, this is not so.

Criteria by which to judge success or failure may be difficult even to define, let alone measure. This is particularly true where the main concern is with "quality of life," as in the stroke trial already discussed. It is, however, probable that trials such as this one will increase in number because, for example, of mounting concern with the problems of the elderly and the disabled. Unfortunately, the record regarding the development of "soft" outcome measures that have general applicability is not very good [14]. The pursuit of these measures could become too much of an end in itself, to the exclusion of any trials at all. Many trials of health services will, therefore, have to derive and validate their own measures of outcome, depending on the particular topic. Where possible, it may be useful to incorporate several measures. We are entitled to be guided to some extent by common sense. If all the measures alter in a direction that experience suggests is toward improvement, it is indeed likely that improvement has occurred. The "right" stay surgery trial [10] illustrates this point. There were no deaths or hospital readmissions—"hard" data. But all the "soft" measures, e.g., residual pain, return of appetite, and restarting work, were consistent in showing that the "right" stay group had done at least as well as the "fixed" stay group—in some ways, a little better.

Blindness—Policy on Results

Many health service trials cannot be double- or even single-blind; both the therapist and the patient are bound to know what treatment group the latter is in. In fields where views about the value of therapy are often held with high degrees of conviction, biased assessments are too easily made. It may be possible to have the assessments carried out by others who are not involved in the trial, but even this solution will often not be entirely satisfactory. An assessment therapist cannot work in the same department as the treatment therapist for a matter of weeks or months and remain ignorant about a patient's regimen. Transporting patients to different departments for treatment and assessment raises other difficulties. Where possible, instrumental methods of measuring progress will be helpful, but they are not always available or relevant.

It is increasingly the practice—even in double-blind drug trials—for the main results on outcome not to be generally disclosed until a definite beneficial or harmful effect has emerged. This is an important safeguard against bias during the remainder of the trial, especially where the trial is not double-blind. If early but inconclusive indications in favor of one treatment become generally known, subsequent results may be influenced. There must always, of course, be a group of two or three who are not directly involved in treatment or assessment who know the results as the trial goes on and who can take a previously agreed course of action if clearly beneficial or harmful results emerge while the trial is in progress.

Implementation of Results

The question of result hangs over trials that successfully surmount all these and other hurdles. A detailed analysis of this aspect is beyond the scope of this chapter, but it would be wrong to ignore it altogether. Particularly where a trial has been undertaken with direct support from an agency responsible for providing health care, or with its active encouragement, it can be argued that there is a strong obligation on the agency to consider at least the practical health service implications. It is hardly reasonable to ask patients to take part in a trial, often at some inconvenience, unless some potential application of its findings can be discerned. On the other hand, health service trials, like any other, need peer review and criticism; and some will not have any impact for reasons that emerge during the process. Financial constraints may prevent the implementation of the results of even good trials. The process of "technology transfer" has been reviewed by Sherman [15], who also suggests that the extent to which useful results lie about unused is a good deal less than is often thought. However, some trials' results are no more than an indication for other studies. It is often claimed, for example, that the demonstration that postoperative hospital stay can often be much shorter than is usually the case could and should result in a rapid clearing of waiting lists. But this is far too simple a view. If hospital stay is shortened, surgical throughput can only be increased if there is a considerable extra provision of operating room time, anesthetic cover, etc. In addition, showing that early discharge is possible for some patients does not imply that it can automatically replace conventional periods of stay for all patients. In the "right" stay study [10], for every patient who was eligible for early discharge there was another who was not, for medical or social reasons that made longer intervals inevitable. Many randomized controlled trials therefore call for other studies—perhaps untidy and not necessarily satisfying ones—aimed at clarifying and dealing with the practical implications of the trial.

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MANAGEMENT OF MULTICENTER CONTROLLED CLINICAL TRIALS

William F. Raub

Multicenter controlled clinical trials require a synthesis of the scientific method and the precepts of modern management. The management tasks associated with these studies are akin to those found in other kinds of complex corporate endeavors. It is recommended that clinical investigators become more knowledgeable about management concepts and methods and management specialists be given a major role in the planning and conduct of large-scale clinical trials.

Controlled clinical trials are fast emerging as a critical link between biomedical science and the health care system. They are applied research conducted fully within the milieu of patient care and are unsurpassed as a means for validating the safety and efficacy of therapies. The results of clinical trials, therefore, are meaningful not only to laboratory and clinical investigators, who hope to see their therapeutically relevant findings applied for the benefit of the ill and the disabled, but also to health care providers, patients, health educators, officials of regulatory agencies, manufacturers of drugs and devices, administrators of health insurance programs, and others who are concerned with the quality of health services.

Although controlled clinical trials vary considerably as to scope and complexity, depending on the disorder and therapies involved and questions being asked, a substantial number of these studies must include hundreds or thousands of patients if there is to be a reasonable chance of achieving statistically significant results. A study population of this magnitude typically is far in excess of the number of eligible patients that any one clinical facility can identify and serve. Thus, a coordinated effort among several facilities is usually the approach of choice. This chapter summarizes the special characteristics of multicenter controlled clinical trials and the issues and opportunities encountered in managing them.

Scientific Management

Like other types of research, the multicenter controlled clinical trial is well-rooted in the fundamental principles of scientific investigation. There is close

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attention to stating the hypothesis and specifying the experimental approach and methods, including various special techniques to guard against biased judgments and actions by investigators and patients. Key methodological issues are generally described in great detail prior to the enrollment of patients in these studies, including:

- The eligibility and exclusion criteria that are to be followed in selecting patients;
- The protocols for administering the therapies that are to be compared*;
- The patient characteristics to be measured at appropriate intervals throughout the study to determine the relative safety and efficacy of the alternative therapies;
- The plans for data acquisition and analysis; and
- The operational procedures for achieving maximum objectivity on the part of everyone involved—e.g., randomly allocating patients to the different therapies and preventing those who examine patients for the purpose of collecting data for the study from knowing which therapy has been administered to whom.

Because the geographical separation among participants in a multicenter trial makes comprehensive manuals of operations and other written communication mandatory, the elements of the scientific method are often more prominently displayed in these studies than in less complicated research.

Similarity to Corporate Management

But the multicenter controlled clinical trial is not only a paradigm of rigorous investigation; it also is a formidable managerial challenge. This class of studies involves multiple performers with varied skills and motivations who are geographically distributed yet committed to a common purpose. As such, a multicenter trial is akin to the complex corporate endeavors that occur frequently in business, industry, and elsewhere in large public and private organizations. Notwithstanding their prominent scientific and medical attributes, large-scale clinical trials offer fertile ground for the successful application of modern management concepts and techniques.

If one looks generically at the question of how complex corporate endeavors are conducted—leaving aside their individual purposes, subject matters, and

*In the interest of brevity, letting a disease run its natural course (in those cases where such action is medically and ethically defensible) is included implicitly in this account as one possible form of therapy.

technologies—one finds a strong recurring theme. Generally speaking, the successful management of essentially any complex corporate endeavor can be said to require the following:

- Objectives that are unambiguous, rigorously justified, few in number, and, whenever possible, quantitatively expressed;
- A detailed "game plan" strongly keyed to these objectives;
- Well-defined responsibilities and interrelationships for the participants (i.e., clear-cut accountability);
- Well-developed communications systems, both within the activity and between it and others;
- Systems and procedures for monitoring progress toward the stated objectives, including milestones that are reasonably frequent, strategically important, and readily determined; and
- Regular assessments of objectives and approach, with a view toward keeping the activity responsive to the potential new opportunities and problems that inevitably appear in an ever-changing social and technological environment.

An excellent exposition of these and other basic tenets of management is given in Drucker's book *Management: Tasks, Responsibilities, Practices* [1].

In the specific case of multicenter controlled clinical trials, one can easily find instances in which each of the foregoing tenets apply and begin to understand the consequences of ignoring them. Moreover, one can identify a variety of events and processes associated with this type of research that are primarily management tasks, even though they obviously involve scientific and medical considerations, including:

- Achieving technical consensus among the investigators and advisers with respect to the study protocol;
- Matching staff and facilities to the tasks at the participating centers;
- Establishing procedures to ensure that patients are well-informed about the purposes of the study and the nature of the care they will receive, as well as their rights and obligations as participants; are accorded high quality care throughout the period of their participation; and are spared unreasonable risks;
- Tracking overall progress of the study, using such measures as patient recruitment and dropout rates;
- Achieving technical consensus with respect to interpretation of the study data initially among the data monitors and eventually among the investigators; and

- Communicating the results of the study to the participating patients, the scientific community, and the public at large.

Indeed, inadequate attention to the management aspects of such tasks can produce deficiencies in a study that are as serious as those resulting from substantive errors or misjudgments about the scientific and medical aspects. Both good science and good management are required for multicenter trials to achieve their objectives within reasonable time and cost estimates.

The Diabetic Retinopathy Study

The organizational complexity of multicenter trials is illustrated by the Diabetic Retinopathy Study [2,3] of the National Eye Institute (NEI). This project was initiated to evaluate "light beam surgery" (photocoagulation) as a treatment for diabetic retinopathy, one of the leading causes of blindness in industrialized societies. To date, the study has shown that this therapy is effective in preventing severe visual loss in diabetics who have relatively advanced pathological changes in their retinal vasculature and in retarding the progression of the disease from its early to its advanced stages [4,5]. The trial is continuing, with the objectives of describing the long-term effects of treatment and comparing the two different modalities of photocoagulation that have been used (i.e., the xenon arc and the argon laser).

The Diabetic Retinopathy Study involves over 1,700 diabetic patients, 15 clinical centers, a coordinating center, and a retinal photograph reading center. The study chairman is a university-based ophthalmologist with special expertise in diabetic retinopathy and clinical research methods. He is assisted by a group of NEI staff members (the NEI project team), an executive committee made up principally of selected study participants, and a variety of intrastudy committees concerned with such topics as clinic monitoring, natural history data analyses, and scientific publication of study findings. The study chairman and the NEI project team, in turn, interact closely with a data monitoring group and a policy advisory group; none of the data monitors participates in caring for study patients or in collecting study data, and policy advisers are not involved in any way beyond their role as counselors to the Director, NEI. Final responsibility for the study, including such major decisions as changing the protocol in the light of interim findings, rests with the Director, NEI. Figure 1 summarizes the functional relationships among these several groups and individuals. Those activities that are principally management tasks tend to be concentrated in the components symbolized by the enclosures with curved sides.

Figure 2 shows the composition of the NEI project team for the Diabetic Retinopathy Study. The project officer, a senior epidemiologist, is the leader of the group and principal spokesman for the NEI with respect to the study. The co-project officer, a widely experienced management specialist, is responsible for not only fiscal and administrative matters but also for a substantial

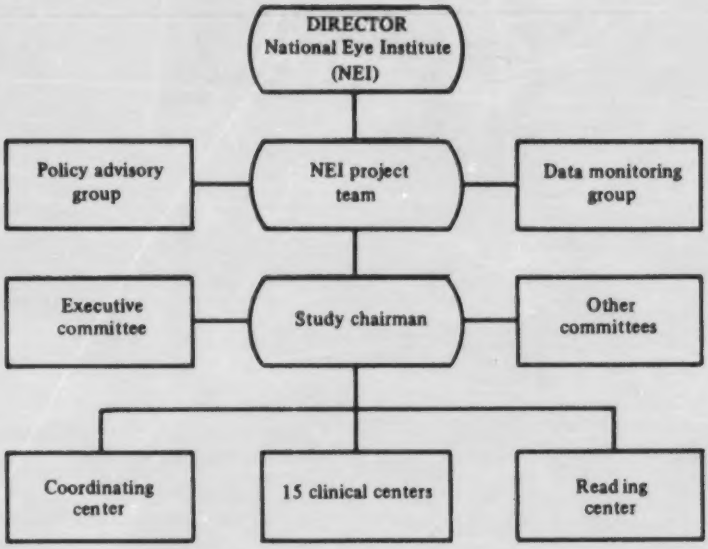

FIGURE 1. The Diabetic Retinopathy Study: Functional relationships

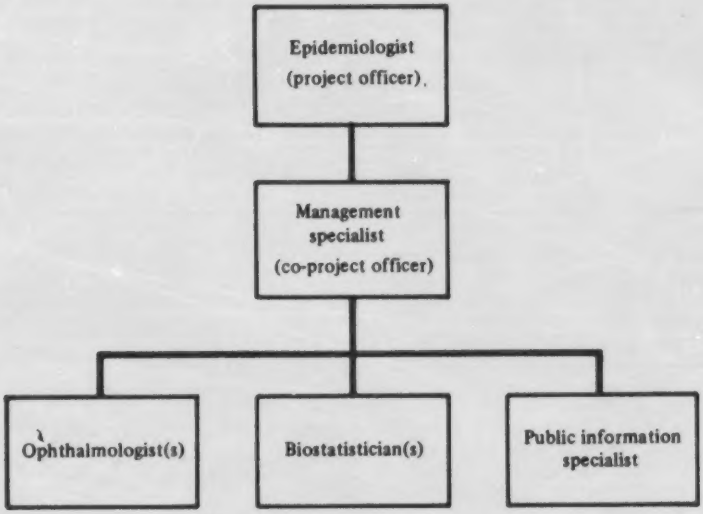

FIGURE 2. The Diabetic Retinopathy Study: NEI Project Team

portion of the day-to-day operational activities in support of the study chairman and the participating centers and advisory groups. The other project team members contribute a wealth of expertise in relevant areas such as ophthalmology, biostatistics, and public relations and information methods. This ad hoc, task-oriented cadre of individuals drawn from various operating components of the NEI has many of the attributes of the new product development teams that are commonplace in industrial management and has been an efficient and effective forum for planning, coordinating, and evaluating study activities. In addition, by accommodating multiple ophthalmologists and biostatisticians as such opportunities appear, the project team has proved to be an excellent on-the-job training mechanism for individuals interested in learning the methods of controlled clinical trials.

On the basis of our experiences with the Diabetic Retinopathy Study and other multicenter controlled clinical trials, the senior staff of the NEI believe that the management aspects of such studies deserve much more attention than they have been traditionally accorded. Furthermore, we conclude that

- Multicenter clinical trials require a synthesis of the scientific method and the precepts of modern management;
- Clinical investigators should become more knowledgeable about management techniques; and
- Management specialists should have significant involvement in the planning and operations of multicenter clinical trials.

If these considerations are made a prominent part of the design and conduct of multicenter trials, we are confident that much can be done to assure high-quality results of considerable scientific and social importance, while reducing the interval between concept and conclusion to the minimum that is realistic and maintaining the costs within acceptable limits. With so many facets of the health care system so much in need of the best that biomedical science can offer, we could have no more compelling calling.

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DISCUSSION

Robert Gordon

Dr. C.C. Booth reported problems in recruiting and educating scientists for clinical trials work. The pay structure for clinical practice is higher than it is for research, and he can only get research workers by offering exciting research opportunities. In addition, where large clinical trials are concerned, research workers often feel they are just cogs in huge wheels.

Dr. Meade shared Dr. Booth's feelings. He uses a variety of methods, including advertising and trial and error, to attract scientists. If we can solve this problem of recruitment we will improve the quality of trials.

Dr. Raub said that the project team concept, as used by the NEI, has given investigators experience in the epidemiological and biostatistical methods and principles of clinical trials. Many of these investigators have then taken this experience and developed their clinical trials.

Dr. D.R. Laurence asked Dr. Meade about the trial of home versus hospital treatment after myocardial infarction. Did the patients consent to the principle of that trial? If so, what were the difficulties? If not, what was the justification? In certain situations, it may be unethical to describe a study to patients.

Dr. Meade answered that his only knowledge of that trial was from the published reports, which say that the nature and purposes of the study were communicated to the patients and their relatives. He acknowledged the particular difficulty in getting "informed consent" in circumstances where the patient is upset and at a disadvantage. This trial did show that questions formerly considered unethical to ask can, in fact, be asked; and the answer can be of benefit to patients.

Dr. Laurence said that in such studies it is perhaps wrong to attempt to get consent, either from the patient or his relatives. This would apply to studies of intensive therapy. On at least one occasion, an ethical committee agreed with this position.

Dr. W.E. Waters suggested classifying randomized clinical trials. In particular, they should be classified as trials that address either of the following:

1. Does the intervention work in an ideal setting, such as a center of excellence?
2. Does the intervention work in practice (e.g., studies that look at the efficiency of the health service system)?

Optimally, both kinds of trials should be done, first to look at effectiveness in an ideal setting and, if the intervention is effective, then to look at efficiency. Most of the time, we need to decide at which aspect the trial is directed to avoid much of the confusion currently surrounding clinical trials.

Dr. Raub noted that most trials are performed at tertiary care centers. These attempt to offer an ideal care situation, but fall far short. They are not research settings but are in the mainstream of care delivery. These studies, while as rigorous as we can make them, are part of the fabric of care delivery.

Dr. Meade said that the Medical Research Council had a vigorous debate on this subject with regard to the hypertension study. In that instance, the majority felt it important to test whether the drugs were of benefit under the best possible conditions, rather than to test outcome in an ordinary general practice situation. It was acknowledged that subsequent trials of the other sort might need to be run.

However, the distinction between the two kinds of trials is not always clear. Much information on delivery of care can be obtained from studies of effectiveness of pharmacologic agents. In trials of remedial therapy, problems of care delivery are so difficult that testing under ideal conditions may be of limited value, since ideal conditions can never be produced in a health service setting. These trials produced in a health service setting are, therefore, being conducted in ordinary service departments.

Dr. C. Meinert pointed out that Dr. Raub's list of factors important to multicenter trials is essential to any large clinical trial. All quality data collections, be they multiple or single center in nature, require attention to these factors. Dr. Raub agreed. He said that communication problems demand these disciplines in multicenter studies, but they should be applied universally.

Part 3

PROBLEMS OF LONG-TERM RECORDKEEPING

Gilbert W. Beebe

The medical record is an essential tool in clinical and epidemiologic research, but some problems of recordkeeping are inherent in long-term studies. Among these are the content, design, and the physical form of the medical record; the quality of the recorded observations; followup procedures; and the use of data for other than original purposes. However, there are other problems of a more threatening nature that currently loom and do not as easily lend themselves to solution. These conflicts grow out of society's escalating concern with privacy and the confidentiality of medical records and its unwillingness to exploit fully and systematically existing record resources to learn better how to prevent disease. The rights of the individual must be balanced against the needs of society in attempting to find a solution.

The medical record is an essential tool in clinical and epidemiologic research, especially in long-term studies. Yet it is only in the last 15 years that medical literature has reported much about medical records per se. Now we have hundreds of papers on medical record systems, medical information systems, medical record science, automation of medical records, clinical data banks, and the like. For the most part these reports are concerned with the adaptation of computer technology to the medical care situation. To many authors the structure of the conventional medical record has seemed ill-suited to automation, and the medical record is now being critically studied in relation to the purposes it serves, especially in teaching and medical care.

L.L. Weed has been a leader of this effort since his 1968 article outlining the "Problem-Oriented Medical Record" [1,2], and a new contender is the "Time-Oriented Medical Record" [3]. Neither of these new approaches to the medical record, nor any of the schemes for automating medical records in hospitals and clinics, offers much benefit to the researcher whose concern is long-term

followup studies or therapeutic trials. This is because the researcher has, however imperfectly, long been accustomed to designing and maintaining individual records in the service of unique purposes. And the researcher was probably using automatic data processing (ADP) equipment long before the university hospital had any use for a computer other than for accounting and billing.

The clinical investigator and the epidemiologist engaged in long-term studies have had some hard problems to deal with in medical records, however. For the most part the solutions are not easy. They require detailed advance planning, pilot work, continued vigilance, and long-term personal commitment.

But there are other problems, and needs, that are new, newly urgent, or now looming large on the horizon. These relate to such matters as the protection of human subjects, privacy and confidentiality of medical and related records, and linkage of existing records in the interest of more efficient use of our resources for answering urgent questions about health and the control of disease. Some of these problems are an outgrowth of increasing national awareness of the potential of the computer for exploiting consumers and invading privacy, and of the increasing reluctance of the public to place its trust in the benevolence of government officials and scientists [4-6]. Coincident with the reassertion of the rights of the individual citizen, however, is the increasing realization that our technologic progress, while eliminating or moderating some health hazards, has spawned a whole new array of dangers to health that we are ill-prepared to identify. So many of these potential dangers appear to result in common ailments many years after initiation of exposure, ailments that are difficult to attribute to their true cause without careful epidemiologic study. Also, the materials for study are often not available. What is needed is access to our human experience on a broad scale and in systematic fashion. This need is directly opposed to current concerns about privacy and protection of human subjects, but it must be articulated if we are to have access to the only experience from which we can hope to learn how to control certain hazards. We must devise social policy and procedures under which research proposals can be balanced against the loss of privacy that research might entail [5]. Simultaneously, we need improved procedures to minimize invasion of individual privacy during such studies.

There are two groups of medical record problems: (1) those that I consider inherent in long-term studies, and (2) some that are new and threatening. I arrived at my conclusions largely on the basis of experience in medical follow-up studies beginning with contraception [7] in the 1930's. Other programs of followup and epidemiologic studies in which I have engaged include that of veterans [8] at the Medical Follow-up Agency of the National Research Council and the A-bomb survivors in Japan [9]. In addition, I have drawn upon the experience of some of the larger long-term studies, especially the Framingham Study [10] and the Perinatal Study [11], as well as the general literature.

Some of the characteristics of long-term studies that seem to affect medical records are (1) the number of institutions generating the records of interest; (2) whether the records are created for specific research purposes or as part of unrelated medical care; (3) whether the study is of the cohort or case-control variety, and, if a cohort study, whether it is prospective de novo or historically; and (4) whether examinations are performed serially or at only two points.

Problems Inherent in Long-Term Studies

Content, Design, and Physical Form of Medical Records

The content of a medical record should be determined by purpose; ideally every recorded item should have a known role to play in the management of the patient, in followup, or in the analysis of results. Without such close articulation of record content and research purpose the investigator risks redundancy as well as insufficiency of information. Yet the investigator is often in the situation where there are several tests, all measuring the same function. If there is no ready way of determining that one is sufficient, the several observations will have to be taken. This situation also occurs when investigators at different institutions each have preferred methods of observation or evaluation and there is no consensus on a single method [12]. In a short-term investigation the cost of redundancy might not seem important, and it might also retrieve missing information. But in a long-term study these deficiencies can be costly and severely limit the conclusions to be drawn from the work.

A standard observational data base is essential, for example, in a cooperative clinical trial of therapy [13]. But a rule regarding data entry should not be so rigidly enforced as to deny a center the opportunity to make special observations of particular interest to its staff provided it interferes in no way with the integrity of the trial. In some instances supplementary observations could illuminate reasons for results eventually obtained [14].

During any long-term study there are likely to be changes in technology and in investigative interest or point of view that seem to require corresponding changes in the set of observations originally determined. The content of the medical record might have to be changed, but it is important that those changes be additions or amplifications that do not destroy the comparability of the original observational set over time.

In retrospective studies or others in which the investigators are not in a position to control the content of the medical record, pilot work with representative samples of records is essential to determine whether the required information is present. For example, in doing the pilot work for a proposed followup study of men with a diagnosis of rheumatoid arthritis in World War II, it was determined that the observations on which the diagnosis was based would not satisfy enough of the criteria of the American Rheumatism Association. The study was voted down.

It should be noted that an interagency committee of the Federal Government, acting pursuant to a recommendation of the National Research Council and the National Archives Service [15], standardized medical record forms to be used by U.S. Government medical facilities shortly after World War II. This step has been of great advantage in studies of medical records created in military, Veterans Administration, and Public Health Service hospitals since that time.

In long-term studies it is especially important that the medical record include the subject's signed consent form in its most current form, reflecting changing requirements of the study and changing regulations. The medical record should also contain information on proposed followup procedures, as these could involve contact with relatives or friends, use of credit agencies for tracing, and the like.

Design of a medical record is only partly a matter of convenience in recording and in data processing, for the research record can also be used in the management of a patient's care, although the requirements of medical care might conflict with those of the research. The significance of records design for long-term studies is precisely the same as that for short-term studies, except that the burden of wrong decisions is greater in long-term studies. Extensive pretesting is necessary for both. The design of the medical record receives a great deal of attention at the present time, but the issues pertain chiefly to the medical care situation, not to research, and especially not to the needs of long-term studies. The researcher has usually preferred to create a record that may derive in part from the record of the patient's care but is physically separate and arranged to suit the convenience of information gathering. The chief practical problem has been to minimize editing and coding costs, and the solution has generally been a precoded format in which abbreviated codes are printed on the form and code positions marked for ready punching [11]. But in addition to the item-by-item record of the patient's situation at a particular examination, many investigators have insisted on a word-picture that integrates all observations on the patient in a more traditional way.

In the cancer registry and end-results programs of the National Cancer Institute (NCI) it was decided not to require a common medical record but to standardize at the level of punch card and tape design [16]. In this way each registry agrees to provide the required information according to the agreed-upon definitions and classifications and to transmit it in coded form to the processing center for editing, collation, and analysis.

Because the long-term research effort almost invariably involves tabulation, the physical form of the medical record usually includes a tape-record version of the paper record. Although many hospitals have experimented with systems in which information is entered directly into the computer from a terminal without a paper intermediary, a paper record still seems necessary. Even where, for example, the laboratory data go on the computer directly, the investigator

will want a printout added to the paper record. Where records become voluminous, storage is limited, and records are constantly in use, microfiche may be considered, but I have never seen this in operation. It was briefly considered at the Atomic Bomb Casualty Commission at one time but was not pursued because of its cost and the uncertainty of its acceptance by physicians in the clinics.

Quality of Observations

It is far easier for the investigator to specify the requisite set of observations than to ensure their quality, although most of the difficulties experienced in ensuring that observations are valid and reproducible are not unique to long-term studies. The latter do, however, have some problems of their own, principally because time is the matrix of change. Those problems are further magnified in collaborative studies.

In the absence of carefully prepared definitions, criteria, and procedures [11], observations will not be entirely comparable. No matter how carefully prepared the manuals in which they appear, unless quality control procedures are applied not only in the laboratory but also in the clinic, there is no guarantee that the observations made years earlier are comparable with those made today. However well observers are trained and rehearsed at the outset, unless the same effort is maintained throughout the life of the project, there will be drift and deviation. Yet without continuity of leadership it is difficult to maintain such a level of control over years.

At the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, for example, comprehensive programs of clinical surveillance were attempted twice before the present Adult Health Study, begun in 1957, gained an apparently permanent place in the overall program of the Commission (now the Radiation Effects Research Foundation)[17]. In recent years, moreover, in response to the emergence of carcinogenesis as the major focus of the Commission's work, the role of the biennial clinical examination as a surveillance strategy has been challenged, and its primacy has yielded to studies based on the death certificate and tumor registries to employ a much larger sample. Although that study is guided by a detailed protocol and medical record forms have changed little in 20 years, only in the laboratory has it been possible to maintain reasonably high and uniform quality in the observational data [18]. There has been too much instability of clinical staff, night clinics have been staffed by temporary, part-time examiners, and there has been too little supervision of the entire process to maintain the uniformity and quality of observational data that one would like to see.

In the much smaller Framingham Study of arteriosclerotic and hypertensive heart disease, begun in 1950 [19], a higher level of quality has apparently been maintained despite some similarities in the rapid turnover of the junior examining staff. In the Framingham Study the senior staff members remained stable,

comprehensive weekly chart reviews were held with three or more physicians participating, and a second physician usually reexamined each patient, especially when the first examiner had a positive finding of major interest [20]. In part the difficulty of maintaining the quality and uniformity of the observations at a high level over long periods of time roots in a failure to appreciate the importance of documentation. Again, the laboratory scientist does better here than the clinical observer in recording procedures.

In the Perinatal Study [11] workshops were held for observers in the collaborating centers, a training movie was created for the neurologic examination, physical examinations were performed blind, and repeat examinations were performed periodically on a sample of patients by observers from other centers. Despite these and other devices to standardize observations and to ensure their quality, the project came under severe criticism in this respect by ad hoc review groups, chiefly because (1) the grant mechanism of support permitted only a committee-type leadership where strong, central leadership was essential, and (2) there was little preplanning for the eventual analysis of vast amounts of data in relation to the multiple objectives of the study.

In long-term studies based on clinical records of medical care the average quality of the record base tends to degenerate following the initial active period of diagnosis and therapy [21-23]. For example, Meadows et al. [22] found that hospital records were adequate for the ascertainment of a second tumor in a sample of long-term survivors of childhood cancer therapy, but not for other changes of clinical interest. With lengthening followup, examinations became more cursory, focusing chiefly on the anatomic region of the original tumor. Kurtzke et al. [23], following U.S. Army veterans with an Army World War II diagnosis of multiple sclerosis, found that routine Veterans Administration (VA) records generated by medical care and compensation considerations became progressively less complete as length of followup increased, unless there was an exacerbation or other acute situation. During periods of little or only slowly progressive change records were often incomplete. Similar tendencies have been noted in longitudinal studies of growth and development [24].

In the NCI cancer registry programs a number of quality control devices have been employed [16,25], including:

1. Development of unambiguous definitions, detailed manuals, and standard nomenclature;
2. Computer edits of incoming data;
3. Field visits, with reabstracting of sample cases from the original hospital;
4. Workshops for training personnel;
5. Cross-check on case finding through systematic use of death certificate files, hospital pathology and radiology department files, central pathology laboratory files, and the like.

A recent development is external monitoring, in which a second coordinating center receives all the input, edits, and error messages to the main coordinating center and handles the data in parallel, including statistical analysis with a free choice of method.

Followup

The success of any long-term study will depend in large part on the completeness of its followup methods, not only because of potential loss of information but also because of possible introduction of bias into the main comparisons of the study by an incomplete followup. It is rare that the investigator has reliable information on the nature of any bias arising from incomplete followup, much less any way of coping with it. Consequently, the less complete the followup is, the more doubtful are the findings reported.

Although a considerable amount of reliable followup procedures are done, they are seldom reported in an informative way. A recent exception is Boice's account [26] of his successful effort to ascertain breast cancer in 1,764 young women treated in 1930-54 for pulmonary tuberculosis with pneumothorax monitored by fluoroscopy. Building on an unpublished manual prepared in the Division of Radiological Health of the U.S. Public Health Service (USPHS) [27], Boice worked out a general method in a pilot study on 25 women. In 3 years he located all but 6 percent of the women treated 20 to 40 years earlier. In his unusual report he specifies tracing sources and evaluates their contribution to his study.

Followup activities do not enjoy high priority in medical research. They are ordinarily performed at a clerical or secretarial level without high standards being demanded. An exceptional influence has been that of the American College of Surgeons [28] in its long-term campaign to encourage hospitals to establish and use cancer registries. For many years the college has established standards for cancer registries and emphasized the importance of followup. The computer has also been of considerable assistance in systematizing followup and increasing its effectiveness [29]. The Mayo Clinic has held to a very high standard of followup, and its medical records constitute an increasingly valuable resource for long-term studies [30]. Military medical records of war veterans are retained under the supervision of the National Archives Service and also provide a major resource for long-term studies [8].

The followup process extends far beyond the domain of medical records, of course. But the question being considered here is: What role does the medical record play in followup? Initially it serves as the source of clues as to the whereabouts of the subject. The longer the study the less immediately available the subjects will be. This fact should be planned for, and at the outset identifying and descriptive information should be obtained with a view to its usefulness in followup. In the Perinatal Study [11] women were chosen whose followup potential seemed superior; most protocols for clinical trials contain similar

provisions for selecting subjects. In his followup study on the late effects of thymic irradiation, Hempelmann has made good use of the names and addresses of parents, siblings, and of two close friends or relatives who would always know the whereabouts of the subject [31]. In the Framingham Study each subject was asked to furnish the names and addresses of a relative, a friend, and a physician who could be expected to know his or her whereabouts at all times. Although there is much confusion on the matter at this time because of the great concern with privacy, it is clear that the Social Security account number (SSN) belongs on every record for which there is a possibility that mortality followup may be attempted later.

Medical records are also important as objects of followup efforts. In prospective studies done in retrospect (in which the starting-point is in the past, and cohorts are traced forward) hospital and other medical records may provide the chief source of followup information. Even in a prospective study begun in the present with subjects expected to be available for periodic examinations in the future, some of the information desired might be in medical records elsewhere and such records might provide insight into the nature and extent of followup bias. The key issue with respect to medical records created elsewhere is their availability: (1) Can the investigator learn of their existence and whereabouts?, and (2) Can the investigator gain access to them? Until recently only the first question was troublesome: once the investigator knew where to find a medical record, there was little difficulty in obtaining access to it on a confidential, professional basis. Following passage of the Privacy Act of 1974, which pertains to record collections of the Federal Government, and increasingly in response to State legislation, it has become very difficult to gain access to medical records created elsewhere, even when requested for confidential research purposes only. This problem is treated more fully below.

I would be remiss if I did not speak of the importance of taking special precautions to ensure the physical safety of records in any long-term study. I speak with some feeling about this because of two unfortunate personal experiences. The diagnostic index to the Navy World War II medical experience was destroyed without regard to its long-term usefulness in medical research, and in 1973 a fire in St. Louis destroyed about 80 percent of the individual Army records of World War I, World War II, and the Korean War already retired to the record center there and not out on loan to the VA.

Use of Data for Other Than Original Purpose

Just as important work can sometimes be done with medical records created only in the interest of medical care, so it sometimes happens that records created for one research purpose can be made to serve another. The conventional teaching is to the contrary; i.e., unless the data were created with a given

purpose in view they are likely to be of little use. But this counsel is too sweeping and ignores some infrequent but real opportunities that should be seized. In its 1945 report, the National Research Committee (NRC) on Medical Records [15] reviewed the research potential of the military medical records accumulated in World War II and concluded that their value for medical research was limited and would not justify a major expenditure for indexing and collation. Although observing that retention of these records for administrative purposes would still make it possible for an occasional followup study to be done, the committee underestimated their value for followup and especially epidemiologic research. In the very next year a different NRC committee recommended establishment of a research program of medical followup studies based on those same records. The subsequently established NRC program of medical followup and epidemiologic studies on veterans has made successful use of these records without any special management procedures for research purposes [8].

The informational needs of our society are now so great that careful studies for one purpose often hold interest for another. The Framingham Heart Disease Study has unexpectedly proved to be a useful source of information on diseases of the eye [32]. The Adult Health Study of A-Bomb Survivors has provided information for a comparative study of cardiovascular and cerebrovascular diseases in Japanese living in Japan, Hawaii, and California [33]. Although the Perinatal Study was originally planned to provide only 7 years of followup, further tracking of individuals with particular characteristics, exposures, etc., is being considered for a variety of new purposes.

Current Problems and Needs for the Future

We who serve the informational needs of society must pay more attention to our resources and to the restraints that are increasingly being placed on our access to them. Although technological change favors our purpose, concern for privacy is on the increase. Legislation is being hastily enacted at both Federal and State levels with insufficient regard for its effect on our ability to learn from our recorded experience.

Rights of the Individual

Our society requires each individual to relinquish some measure of privacy and freedom in return for the benefits society affords. But lately we have been impressed by the rapidly growing capacity of Government and large organizations to accumulate and exchange large amounts of information about individuals via the computer. We also have been confronted by evidence of persons in power using that information against individuals. There is a widespread distrust of large organizations and of Government, and our representatives in the

Congress and in State legislatures are taking active steps to curb the process of creating data banks that might be used to curtail individual liberty [4].

We are also increasingly sensitive about the treatment of human beings as objects and have strengthened our ethical codes for the conduct of medical research on human subjects. Medical records often contain personal and intimate information that must be shared among those with responsibilities for professional care in the medical situation. They have customarily, by extension, been used in medical education and research with no suggestion or fear of public disclosure. But with varied and complex schemes for paying the cost of medical care, for medical audit, and the like, the number of people with an apparently legitimate right to know the content of the record is increasing, and the need for strict rules of access is generally felt.

Our attitudes toward medical records are changing very rapidly but a new synthesis, adequate to the needs of the times, has yet to emerge [5]. The safeguards of medical ethics no longer seem suitable, and we are searching for legal and administrative safeguards to replace them. Meanwhile, the investigator must contend with uncertainty and conflicting requirements that hinder access to information. The burden is especially heavy for investigators engaged in long-term clinical or epidemiologic research because of their frequent need for access to records created outside their own institutions.

When the Privacy Act of 1974 severely restricted access to individually identifiable Federal records without the prior consent of the individual, responsible administrators began to respond unfavorably to requests for medical records for research purposes. This trend has progressed and in many States has been strengthened by legislative restrictions [34]. There are now more laws and litigation concerning medical records than ever before. Although there has been no legislative intent to hinder research, there has been insufficient understanding of the need for access to individually identified medical and related records on the part of investigators, especially those engaged in long-term research.

Perhaps, however, some progress is being made. Whereas the Privacy Act limited the researcher's ready access to Federal records on individuals, the Privacy Protection Study Commission created by that act has recommended that the research interest in records be given some privilege [6]. The Commission has accepted the basic distinction between the administrative or service use of records and the research or statistical use in which the individual remains anonymous and has recognized that the corresponding risks to the individual are of a different order. The Commission recommends disclosure of medical records, without explicit authorization of the individual, for use in biomedical or epidemiologic research, provided that certain conditions are met: that the recordkeeper determine that disclosure in identifiable form is necessary for the research; that the recordkeeper determine that the importance of the research is sufficient to offset the risk to the individual's privacy; and that the researcher take adequate steps to protect the information from

further disclosure. While the recordkeeper must bear the ultimate responsibility for disclosure, one would like to see the researcher's request accompanied by supporting statements from an institutional review board and a funding authority to assist the recordkeeping agency materially in making its decision.

At a number of other points the recommendations of the Commission would limit the capacity to perform long-term followup and epidemiologic studies. In her American Association for the Advancement of Science presentation Robins [35] stressed the following points that need further consideration toward balancing the individual's right of privacy against society's need for more adequate information with which to maintain health and well-being:

1. Recognition that it is not only medical records that may be needed in a medical investigation but also records of many other kinds, especially in behavioral research and in studies of diseases for which incidence, treatment potential, or outcome is conditioned by lifestyles.
2. The brevity of the recommended period of authorized access to records used in research; long-term studies need long-term access.
3. The recommended limitation of the disclosure of information necessary to accomplish the purpose for which the disclosure is made—a suggestion that seems to make the recordkeeper responsible for screening and abstracting records for the investigator. This is a function that could not be expected to be performed efficiently and that could easily prove so onerous as to discourage compliance with the request for disclosure.
4. The recommendation that no further use or disclosure be made without the approval of the original recordkeeper. For long-term studies this recommendation poses real limitations, as the need for further followups often cannot be anticipated. Findings from the first study may require that a different but related study be undertaken with the same material, and over the long term the identity of the original recordkeeper could be obscured by organizational changes.
5. The recommendation that disclosure be conditional upon an adequate program for removal or destruction of identifiers. This can be a very serious restriction for long-term studies, there being too many unanticipated situations arising from within a study, or from other investigations, that require a further look at the material or some part of it.

The Commission could cite few examples of serious invasions of privacy or mishandling of confidential information during the course of medical

investigations. The ethical principles guiding investigators have been an extension of those governing the relationship between patient and physician, and they have worked very well. Nevertheless, more attention needs to be given to the procedures that investigators actually use to safeguard the privacy and confidentiality of the information entrusted to them because the volume of long-term research with human subjects is increasing sharply, nonphysician investigators are becoming more frequent, and law is replacing ethics as the means of social control. To acknowledge the ethical principle that "no harm or distress will ensue for the individual and his family, and that the doctor-patient relationship will in no way be impaired" [36], and to inculcate among one's staff adherence to this principle are no longer sufficient. Procedures that extend beyond the development of programs for safeguarding data in computer format are required to minimize the risks of untoward disclosure:

1. Matters of forms design;
2. Early assignment of a study number to replace the usual identifiers;
3. Storage of data;
4. Selection of information to go on computer tapes;
5. Selection and training of personnel;
6. Securing signed pledges of confidentiality from all personnel with a need to handle individually identified information; and
7. Extension of security precautions to any subcontractor or other agent sharing access to the information.

Within the area of epidemiology this need has been well presented recently by Gordis et al. [37], who also stress the importance of emphasizing both principles and procedures in the academic training of individuals for research careers. The research community and the professional societies can do more to develop such procedures and to ensure their use, but administrative regulations and surveillance might also be desirable. Most long-term medical research is performed under grants and contracts from Federal, State, and private agencies and thus can be brought under administrative control, if necessary.

There is another side to privacy and the public interest represented by the Freedom of Information Act of 1967, a legislative effort intended to open the process of Government to public inspection. A government agency must respond promptly to requests for documents relating to its operations. The implications of that act for longitudinal research are potentially threatening. Subject to interpretation in the courts, the act might be used to obtain the records of ongoing research even before definitive analysis and publication. The usefulness of a study might well be impaired by premature publicity given to preliminary findings. Two suits, one unsuccessful [38], the other pending on appeal, have been filed to obtain the records of the University Group Diabetes Program, which was carried out with HEW funds. In another case [39] the

courts ruled that the National Academy of Sciences was not subject to the act despite its substantial Federal funding. Despite these two decisions, it is not yet clear to me that the investigator performing research under a Federal grant or contract might not be subject to court order to produce records at any time during the course of his work. This is not to suggest that individually identified records are at risk, for the act has an explicit provision protecting them. But records stripped of identifiers might be forced from an investigator's control before all work was done, thereby endangering the study.

Nevertheless, certain key studies could become the basis for medical or regulatory decisions affecting the welfare of millions. Therefore, some reason might exist to put their data into the public domain immediately upon publication of the final report. The National Technical Information Service, U.S. Department of Commerce, has added data tapes to its inventory of Government-sponsored reports for sale and could serve as librarian and distributor of public use files of data from completed studies of continuing national significance.

Since medical investigators who collect record information from diverse sources, or engage in long-term followup, must frequently approach the subject personally or through questionnaire, they must explain their interest in the individual. Either implicitly or explicitly they try not to divulge personal information so obtained. It is my understanding, however, that they have little protection against a subpena requiring release of the information, except under the acts governing the use of records of drug- and alcohol-abuse patients. It would seem desirable that an investigator be able to provide stronger assurances of confidentiality than can now be validly made, as has been recommended by the Privacy Protection Study Commission [6].

The Needs of Society

Although the field of health and medical care is not alone in its expanding need for information with which, it is hoped, our lives may be enriched or extended, great urgency often attends its needs because lives are at stake. These needs are currently amplified by the importance we attach to a reorganization of our medical care system. We are interested in defending ourselves against increasingly smaller risks and influences operating over longer periods of time. Diseases that might have more than a single cause or whose experimental models, while useful, do not substitute for human experience are now our concerns. We feel caught in the grip of a technological growth process that we can no longer equate with progress, so frequent and startling are our discoveries of its ill effects in our hands. We are given reason to fear our food, our workplace, our medicines, our water, and the very air we breathe. Yet our approach to learning about such matters as the effect of environment on health is fragmented and opportunistic, not purposefully systematic.

The answers we seek often lie embedded in our human experience, some of which is already a matter of record. But as a society we have been unwilling to take full advantage of our technologically advanced state because we fear data banks in our free society [4] more than we appreciate what gains might accrue from a carefully controlled linkage of existing files. I am not suggesting that we create vast new data bases or that we extend our recordkeeping to new areas or greater depth. I do not visualize one big system of information ever being sufficiently useful to justify its cost. But I think I see opportunities for the linkage of existing records in the service of medical research, opportunities that are neglected or that cannot be realized because our information needs have never been seen as whole: we have been intrigued by the "1984, Big Brother" apparition. Moreover, in the past several years tools and opportunities for linkage have been withdrawn from the limited array formerly available to us, not because they were misused but because attitudes are changing. There have been abuses of sensitive records for political and other social reasons unrelated to research. If we are going to fulfill the promise of our calling as investigators, we must work to establish a more systematic approach to the use of medical and allied records to solve health problems, while working to devise safeguards against the abuse of record information. This means participating in the current debate on privacy matters in an effort to resolve the apparent conflict between science and the individual.

In two papers advocating more systematic use of record linkage, Doll [40, 41] contended that the confidentiality of computer records can be more easily protected than that of the standard hard-copy records. He stated that he knew of no instance where the provision of personal information to a bona fide medical research worker had led to abuse.

In the area of occupational health, for example, we should be able to do a great deal more than we now do to identify high-risk industries, occupations, and workplaces, since occupation and/or industry appears on so many large files, e.g., death certificate files of the States (occupation and industry), the population census (occupation and industry), the Federal income tax form (occupation), and Social Security Administration files (industry). It should be possible to link enough of these files for a sufficiently large sample of the work force, with appropriate safeguards, to monitor occupational hazards at the level of mortality and disability. Such monitoring would not establish hazards to the satisfaction of either the scientist or the regulatory agency of Government, but it would illuminate areas of potential concern to which methodologically adequate studies could be directed. In this process the SSN could be very useful, although as a unique identifier it seems to have deficiencies [42]. It is unfortunate that the Privacy Protection Study Commission discouraged extension of the use of the SSN, for it is the single most useful number we have for linkage. Lunde points out that many European countries make routine use of such identification numbers for linking files and that such use has not led to the establishment of central data banks [42].

Newcombe, who has been doing record linkage studies for many years, recently suggested monitoring delayed effects of occupational hazards in Canada by linking already existing files, including a 10 percent file of occupational histories [43].

Record linkage to facilitate surveillance of occupational health would be more effective if certain other changes were made, e.g.:

1. If more States were to code the occupational statements on death certificates as suggested by the Technical Consultant Panel to the U.S. National Committee on Vital and Health Statistics [44];
2. If morticians and hospitals were encouraged to use the SSN on death certificates;
3. If more States were to declare cancer a reportable disease; and
4. If there were more uniform standards for the long-term retention of employment records and employee health records.

A beginning has been made in this direction under the Toxic Substances Act, which requires that records of adverse reactions be retained, and under the Occupational Safety and Health Act, which has prompted a regulation that the records of terminating employees, with a history of exposure to certain named carcinogens, be sent to the National Institute for Occupational Safety and Health. Under the terms of its 1976 Occupational Carcinogenesis Act the State of California requires the registration of employees exposed to specific named carcinogens. Without appropriate legislation there is a real danger that employers will destroy employee health records that might be used in identifying long-term health hazards.

Occupational hazards are but one area in which systematic record linkage would be very useful. There are many other environmental hazards to be investigated, as is there a need for long-term monitoring of the effects of new drugs, vaccines, and other innovative procedures. For example, photochemotherapy of psoriasis, now under investigation in a randomized clinical trial in the United States, will apparently require long-term monitoring for possibly deleterious side effects, including blood dyscrasias, melanomas, and other malignant neoplasms [45]. Human exposure to PBB's (polybrominated biphenyls) in Michigan, resulting from the mistaken use of the fire-retardant as a cattle-feed additive, may well require long-term surveillance, although the first scientific report is reassuring [46].

Large cohort studies with mortality as the endpoint have been feasible for war veterans [47], but very difficult and expensive for the population generally, because of the decentralized filing of death certificates in the 50 or more jurisdictions of the United States. In 1968 the U.S. National Committee on Vital and Health Statistics recommended that a National Death Index be established to facilitate such mortality studies [48]. Although the proposal was

greeted enthusiastically by professional societies whose members engage in long-term followup and epidemiologic studies, it was not received sympathetically at the National Center for Health Statistics until recently. Now an ad hoc group is devising a workable plan for such a mechanism to be established in the center. There are innumerable specialized registries in the United States, in addition to a growing number of population-based cancer registries, whose usefulness will be enhanced if the National Death Index becomes a reality. Many of these specialized registries are concerned with new therapeutic approaches, such as organ transplants, that require long-term evaluation. In clinical trials of therapy, also, there is a growing interest in long-term mortality followup that will be much easier and more complete once the index is established.

One of the more unfortunate effects of the Privacy Act of 1974 was the termination by the Internal Revenue Service (IRS) of the address-search service to investigators. Presented with a file of names and SSN's, the IRS had provided "address only" information to qualified investigators at a nominal charge. The 1976 Tax Reform Act later made it illegal for the IRS to perform this service. It was a very important service for investigators engaged in long-term research, especially those doing large studies for which tracing costs tend to be very expensive. It provided survival information and enabled investigators to explain their studies to potential subjects and to request their participation. The subject was always in a position to refuse to participate; any invasion of privacy seemed small indeed.

Another casualty of the recently heightened concern over privacy has been the refusal of Veterans Administration hospitals in most States to continue participating in the population-based registries sponsored by the National Cancer Institute. Despite many efforts to overcome this problem it remains unsolved. The NCI has also not been able to arrange any systematic access to medical records of the Veterans Administration for the purpose of epidemiologic research.

We may soon have a national health insurance system. I urge that, in framing the necessary legislation, Congress will be sensitive to the opportunity to use medical records to produce information needed for the control of disease, not just to pay for its diagnosis and treatment. I hope it will recognize that our need for information is very great, that our present approach is very inefficient, and that it should be possible to minimize risks to privacy and confidentiality.

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PROBLEMS OF LONG-TERM RECORDKEEPING

Raymond Illsley

The maintenance of medical data on a large population over a long period is usually time consuming and expensive. One must ask whether the long-term approach is necessary or desirable and whether usable results could be obtained by more economical methods. A number of large-scale, long-term record systems, maintained for a combination of research and service purposes, are described here, with a special emphasis on the technical and ethical difficulties posed by the practice. Society must both overcome the technical problems and determine the ethical bounds of what is permissible in the way of collation of medical records from diverse sources.

There is something inherently attractive about the comparison of life events over long time periods. Many medical and social problems have a long period of gestation; consequently the search for causes in contemporary or preceding conditions might be fruitless, because such conditions might be only the ultimate manifestations of processes set in motion by events and environments occurring at a more distant time. The timely and selective collection of data today might, in these circumstances, be regarded as investment for the future: today's data for tomorrow's use. Or it could be seen as as an attempt to circumvent history. Usually we prefer retrospective study, the use today of data wisely laid down a decade or more ago. It is rare, however, to find data systematically collected and recorded in the past that meet the precisely formulated scientific needs of contemporary research. Most frequently we find that such data are not clearly focused on our problems, i.e., that terms have not been defined, observations systematically made and recorded, and classifications consistently applied, or that the populations are inappropriate, incomplete, or untraceable. This occurs not merely because our predecessors were thoughtless or unscientific, but also for reasons that apply strongly to prospective study. The future is as uncertain to us now as our present was to our predecessors. The time interval between question formulation and its application a decade hence could render our work irrelevant or unusable. Problems may be solved, or bypassed, data and populations may be distorted by later events, giving the result historical interest without practical applications.

The maintenance of data on a large population over a long period is usually time consuming and expensive. The additional possibility that the uncertain nature of future events will make the exercise redundant, impractical, or insignificant prompts us to ask whether the long-term approach is necessary or desirable and whether usable results could be obtained by more economical methods. The answer depends on the nature of the problem and the comparative effectiveness of alternative approaches. With this caution in mind, I begin by examining research involving long-term recordkeeping before looking in more detail at the problems such recordkeeping poses. My remarks are based on work in which I have participated and are more directly relevant to sociological and epidemiological research than to clinical trials.

The Continuous Census

For over 30 years a data bank was maintained in Aberdeen, Scotland, recording the reproductive events of an urban community of approximately 200,000. It is perhaps the nearest we have come to observing and recording the clinical and social data relating to all the pregnancies, abortions, perinatal deaths, and major gynecological events of a total community [1]. In essence, however, it is merely one example of the most common type of long-term recordkeeping, a continuous cross-sectional recording of individuals experiencing the same events. The population varies, but the topic is constant. It is similar to the universal exercise of the registration of births and deaths. The data bank's aim is to monitor changes over time in reproductive behavior and performance and the distribution of the reproductive event (pregnancy, abortion, perinatal death, sterilization) across the subgroups of a population. Over the 30 years of its existence, the data bank has been used by obstetricians, gynecologists, nutritionists, pediatricians, psychologists, sociologists, and statisticians to examine (and write about) a wide range of issues at both applied and fundamental levels. It differs from national registration systems in the amount of social, demographic, and clinical detail recorded and its use for both research and clinical service. It also differs from many similarly detailed hospital record systems in its attempt to cover a total community continuously over time. But the problems encountered are a composite of those in both national registration and hospital recording system.

First, there are problems in the definition of the population and the maintenance of total coverage of that population. Departures from total coverage would lead to a distortion of results because significant omissions or extensions would invalidate comparison from year to year. The local problem in Aberdeen is simplified because the whole area is covered by a single clinical service. The original research boundary was the city boundary, excluding only a small part of the residential population. During 30 years growth of the residential area extended well beyond the original boundary, and the outer areas

came to contain a highly disproportionate segment of the middle class. Periodically, therefore, it became necessary to extend the boundary and to code and enter into the record system the case histories of those reproductive events occurring in the incorporated area from the beginning of the data bank to the time of incorporation. This is not an example of obsessive recordkeeping. Failure to update boundaries leads to distortion of the trends under observation and, hence, an invalidation of the study's purpose. In our case, it would have shown a misleading stability in those rates of reproductive morbidity related to poverty by increasingly excluding that portion of the natural population of the area least prone, for example, to perinatal death and low birth weight. The ability to update in this fashion is relatively rare; in our case it was possible only because the excluded areas had always been part of the same clinical service. We are nevertheless aware that the retrospective data were less complete and probably less accurate than those relating to the area that had continuously been part of our research area.

Similar problems would arise if there were constant changes in nature of the population receiving service in the medical institutions involved; if, for example, significant and changing proportions of the urban community received treatment elsewhere, or if there had been marked changes in the social ecology of the city comparable with those that so frequently occur in inner cities. Although such trends would not have invalidated the data, they would have rendered interpretation difficult. Moreover, morbidity and mortality rates would not have reflected a representative population but would have mirrored the changing ecology of the city.

The second major problem is the establishment and maintenance of standard definitions and classifications. Professional practices vary considerably in what is recorded, in the signs and symptoms regarded as important, and in the definition and classification of complications, diseases, and outcomes. The problem is least acute in discrete events such as birth and death, or in easily measured characteristics such as height and weight (although an anthropometrist would challenge the latter statement sharply if highly accurate measurements were required and if simple safeguards were not specified relating to calibration of scales and the clothing of the subject). The problem is most acute for subjective judgments about health status, for unverifiable information supplied by the patient (e.g., date of last menstrual period), for complex events such as the process of labor, and for clinical categories requiring professional judgment or a mixture of measurement and judgment (e.g., preeclampsia). The initial establishment of definitions and classifications demands common commitment across the range of professional staff and institutions involved and recognition of the importance of the task. Maintenance over time requires not merely commitment but constant socialization of new staff and vigilance by coding and research staff members to prevent the inevitable tendency to drift. The best safeguards against such drift are an active research team and the involvement of clinical staff in the use of data (it has been our

experience that the quality of data declines if they are not constantly used and if clinical staff do not appreciate the use to which their data are put). The changing percentage of "not stateds" in tabulations is a fairly sensitive indicator of usage and quality.

A third problem stems from the emergence of new procedures and techniques, not merely in medical management but in recordkeeping itself. For example, it was a long time before we noticed that under "type of delivery" the code "other types" was assuming major proportions because we had no code for vacuum extraction. The change-over from artificial rupture of the membranes to medical induction caused similar problems. Classifications refinement becomes necessary with the increased prevalence and variety of previously minor categories, such as abortion and sterilization and the methods by which they are performed.

The emergence of new procedures is paralleled by the new problems, interests, and priorities. Record systems reflect the purposes of their founders and the service and research problems existing at the time of their origin. Perinatal death could yield first place to low birth weight or minimal fetal damage, and grand multiparity could be replaced as a research priority by abortion, infertility, or sterilization. Although items can be dropped, unrecorded detail on emergent problems cannot be recaptured. Research is constantly moving, at least in the perspectives and hypotheses employed, if not in the problem itself. At one point in our study, it became obvious that investigators were using the system less and resorting more frequently to raw case histories because the original topics and hypotheses had been partially exhausted. The data bank was being used only to supply the epidemiological framework within which new and more detailed studies were located. Updating was necessary, requiring efficient methods of case identification and recoding.

Serial Studies

The instances described above involved recording the same phenomena for constantly changing patient populations; the focus was on secular change. The same information could, however, be used to study the succession of events within a single episode, i.e., a pregnancy. The emphasis is thus shifted to the course of pregnancy, to the interrelationship of events from first referral through antenatal care, labor, the puerperium, postnatal examination, and beyond. Many of the problems mentioned above, particularly the maintenance of standard definitions, are still pertinent. Others, however, are reduced because the time scale is shorter, boundary and population changes may be less distorting, and the system can be discontinuous or constantly and radically changed to reflect new interests without damage to the main purpose.

One variant of this logical type, however, can present even more intransigent problems than the continuous census: the attempt to link individual reproductive events into complete reproductive histories (ranging from first

pregnancy to completed fertility, hysterectomy, sterilization, and later gynecological conditions). Boundary and population change become important once again because movement into and out of the record network produces truncated histories. If the movement is selective, cases with complete histories will differ from the remainder, possibly in significant respects that produce misleading results about the relationship between successive pregnancies or between pregnancies and other events such as abortions, sterilizations, and gynecological conditions and diseases. Continuity in the record system as a whole, its topical content, and the definitions used are at least as important as in the continuous census.

A new set of ethical problems could also arise. It can be argued that patients willingly give information on each episode because they see the information as relevant to the treatment of their presenting problem. They might, however, perceive each episode as separate and might, therefore, be uneasy to know that two separate episodes were recorded and linked in a research record system. Certain episodes in a history might contain sensitive elements—premarital or illegitimate pregnancy, abortion, venereal disease, and sterilization have social connotations, some of which are stigmatic. For demographic purposes a history is not complete if we do not have information about second marriages and if we do not trace the patients' whereabouts until the end of the reproductive period—women who do not reappear may have had no further reproductive events, they may be appearing under another name, they may have moved outside the boundary. Moreover, with the increasing occurrence of vasectomy, someone—some day—is likely to suggest that information on women alone is scientifically inadequate.

We have taken the view that our community in general, but not each individual within that community, is aware of our widely publicized research activity. No public protest has arisen, and individual refusal or reluctance to give information is extremely rare. There are preconditions for such trust, to which I shall return later. However, changes in general public sensitivity have occurred over the 30 years during which the data bank has been established and the 26 years with which I have been associated with it; our own sensitivity has increased correspondingly. The danger and the potential problem exist that sensitivity may increase to the point at which the linkage of events over a long period may become impoverished. This problem underlines the parsimonious care with which such linkage should be initiated and the importance of safeguarding the security of the information, but it also indicates the desirability of some form of public monitoring of the principles and conduct of such recordkeeping activity.

Longitudinal Study

My next example, although I describe it as a "longitudinal study," is logically only a variant of the category described above as "serial investigations."

It refers to the followup from birth onwards of a cohort of children drawn from the data bank. The main purpose of the exercise is to examine the relationship of complications of pregnancy, labor, and delivery to the subsequent physical and intellectual functioning of children. Many similar studies have been conducted in the United Kingdom and in the United States [2]. In some cases these cohort studies have stopped at their limited initial objective, but in others the cohort has formed the base for the study of a wider set of issues not necessarily related to pregnancy and perinatal complications [3]. Again, in some studies information has been collected directly from the children and their parents, while in others data from other record systems are collated with the original data set.

Each of these types of study presents a different set of technical problems, but common to all is the problem of identification. Some of the British systems have used National Health Insurance records for tracing individuals whose addresses have changed [4]; others, more locally based, have used school records or electoral rolls. American research workers are more likely than British to use telephone directories, and most have used a variety of sources [5]. Whatever the method, maximum identification is desirable because missing cases are likely to be selectively biased. Children with unusual characteristics might occur more frequently in administrative records, but those unusual characteristics frequently might be correlated with case histories involving adoption, change of name, migration, and institutionalization. Record systems are usually maintained for specific purposes, implying different definitions of the population at risk and categories of exclusion. In the marriage of two record systems, the common core population is at double risk of attrition and imbalance.

Similar risks apply to the quality of data. Information is obtained and stored in record systems for specific purposes, probably unrelated to the research aims of the longitudinal study. It is, therefore, subject to the normal problems of data collection, coding, and storage, as well as to those arising from the manipulation of secondhand material for research purposes.

The remarks made above about identification and tracing have doubtless already suggested the considerable ethical problems involved. Where followup data are obtained directly from the subject, ethical problems are minimal. But where they are obtained by the marriage of record systems, they are being used for purposes for which they were not originally requested; and informed consent is either impossible or impracticable in large-sized populations. Since one of the major advantages of this type of research is its economy (data on a large scale can be deployed without the costs of ad hoc collection), the need to make personal contact to obtain informed consent would quickly dissipate the saved resources. A balance has to be struck between the values of the expected findings, economy, and ethical considerations. Or alternatively, ethical principles as perceived by certain segments of the public need to be reformulated.

Conclusions

For research involving long-term linkage the maintenance of identifiable records of named subjects is essential [6]. Dangers of unauthorized access can be reduced by technical means, particularly by numbering systems with highly controlled access to a master list of names [7].

Unauthorized access is not specifically a problem of research. Records maintained for clinical service purposes are frequently more vulnerable to unauthorized use than research files, particularly more so than computerized data. In good practice, whether it be clinical or research, names are routinely replaced by numbers; and access to manuals, master files, and tapes is restricted to named users.

Categories involving the use of routine data for purposes not specified at the time at which the subject provided the information present different ethical problems. In certain cases it is arguable that patients could be expected to know that information would be used for research purposes and that, therefore, consent was implicitly given. Although the reasoning may be ethically dubious, the case is arguable for the vast majority of women who present for antenatal care and delivery in Aberdeen. Research on a large scale has been conducted on reproductive events for nearly 30 years and has received wide local publicity. The fewest problems arise when research, as in serial study, is limited to the events of a single pregnancy. The patient would have less reason to expect that data from two separate pregnancies would be linked for research purposes and even less to expect that a pregnancy event would be linked with an abortion or a child's educational or delinquency history. Sometimes such linkage is anticipated, and patients can be asked for consent when they provide the information; in other cases, the research population may be small and easily accessible to be contacted directly. Where these conditions do not apply, data are being used without informed consent. Is this ever justified?

The arguments are well known. Many advances in medical knowledge have been achieved by the collation of records from different sources, particularly those which link environmental conditions with morbidity and mortality. Such advances either would not have occurred or would have been delayed if ethical considerations had prevented collation [8]. There are other formulations contrasting the public good with individual sensitivity [9]. My own view has been that what is permissible depends on the trust of the public in its research and service organizations. To some extent, such trust can be obtained or maintained by strict security conditions and by public knowledge that such conditions are enforced. This is a strong argument for the existence of community-controlled systems that monitor the collection and storage of such data, rights of access, and the purposes for which data are used [10].

The need to establish such monitoring systems is, however, evidence that distrust already exists. Sometimes that distrust arises from the misuse of

medical information, but most frequently it stems from misuse of political, commercial, and legal information for power or gain, which, in turn, creates feelings of hostility or suspicion toward any storage of data about individuals, their character, behavior, or history. Our current ethical concerns are therefore an indication of the presence in our society of groups in conflict with each other and with authority—and importantly, of the power of such groups to express their views and enforce their rights. I see no ethical absolutes beyond the injunction not to use data on patients in ways that would harm their welfare, their legitimate interests, or their human rights. The definition of welfare, interests, and rights is, however, the subject of constant moral re-evaluation in light of changing divisions within our societies and conflicting perceptions of personal interests and the public good. The determination of that delicate balance is beyond the individual research worker attempting to use universal guidelines. The ultimate protection must be a community-controlled legitimating agency.

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DISCUSSION

William C. Mohler

Several questions addressed the Aberdeen Study itself:

- Was there significant geographic change in the Aberdeen population through migration over the 30-year span of the study? Dr. Illsley said there was relatively little outmigration during the first two decades. A survey in 1969 showed that about 10 percent of the people born in the 1950-55 period had left the area. Recently the area has had an influx of workers because of the oil exploration in the North Sea, and the geographic stability of the population has decreased. Pregnancy data from the 1950's are not directly relevant to reproductive events in the 1970's.
- Had the study of reproductive events expanded to include studies of sex? No, there were no such studies. Dr. Illsley noted that in long-term studies depending on continued support and cooperation from the community there may be a tendency toward caution in adding any new potentially controversial areas of investigation. Sex per se was not a social issue in the Aberdeen area until abortion became a problem in the mid-1960's.
- Are data from the study available to other research groups, for example, those interested in occupational effects on reproductive events? Yes. The Aberdeen Study would certainly like to see its data be useful to others. They are available with, of course, provision for anonymity of the data and provision for the Aberdeen group to see the analyses before submission for publication (to comment on them from the researchers' extensive knowledge of the study population and the data).

Other comments dealt with general policy issues of personal privacy and the access to records and derivative data:

- There seemed to be agreement that within the medical and research environment magnetic tape records should be less of a privacy hazard than "human processed" materials, such as conventional medical records. Casual nonmalicious access to the latter is likely to cause privacy problems.
- Followup for long-term studies and the occasional need to reach people who have been in short-term studies are of major importance. This has implications for record content, recordkeeping,

and some appropriately controlled means of "linking" to record systems that can provide current addresses for people.

- The British experience to date does not include anything comparable with the effect of restrictions in the United States by the Privacy Act of 1974 on access to medical records for research studies. In part this is due to the United Kingdom's action of central authorities (such as the Medical Research Council) to deal with the problem without new legislative strictures.
- To supplement Dr. Beebe's reference 37, Dr. Klimt pointed out that the legal decision in that case had for the time being protected data in the hands of HEW grantees from access under the Federal Freedom of Information Act.

Part 4

COMPENSATION OF RESEARCH SUBJECTS FOR ADVERSE EFFECTS

J.B. Harman

It is argued that subjects of therapeutic research are essentially patients under treatment and should be compensated in the same way as patients. This means that they will only be compensated for damage that arises from negligence, and the compensation will come from the defense societies (the British equivalent of insurance companies). Other sources of damage are regarded as the inevitable hazards of being ill or being treated, for which there is no compensation. There have been no claims from subjects of therapeutic research to test this view.

Subjects of nontherapeutic research have nothing to gain and should, therefore, be fully compensated for all damage. The defense societies will pay only for negligent damage, so the question arises of who will pay the no-fault compensation. The Royal College of Physicians of London suggested in 1973 that this should be the responsibility of those who promoted the research. Preliminary experience suggests that this will be done.

The United Kingdom's defense societies work differently from the insurance companies in the United States. There are three societies in the United Kingdom, and between them they deal with all malpractice claims. They are not commercial insurance companies with contracts and profits but mutual benefit societies in which members are eligible for certain benefits at the discretion of counsel. This allows the counsels to defend members where their reputation is at stake, even though it would be cheaper to settle, and to spend money maintaining the good repute of the profession and in giving advice on how any proposed new legislation might affect the doctors' responsibility. Membership is secured by an annual subscription for doctors whose work in any way affects patients. The total membership is 150,000, which includes dentists and overseas members from States formerly under British rule (approximately 5,000).

I have no experience organizing research, but I consider my thoughts salient here because the requirements of defending research workers and compensating damaged subjects should in no way interfere with the way in which research is carried out. There are plenty of restrictions as it is on research. It would be meddlesome to introduce an element of defensive research analogous to defensive medicine. This view is in accordance with the general attitude already held by the defense societies in the United Kingdom toward medical

practice. It is not for us to say what our colleagues should or should not do; our job is confined to getting them out of trouble when they get in.

My experience of claims arising from research, however, is limited to five cases, which can reasonably be said to be no experience at all. But no one in the United Kingdom has more experience, for these are the only known cases ever to have been brought, dating back as far as William the Conqueror.

Claims are not the only things that we have to deal with. There is also anxiety about claims, and this anxiety is widely felt by those who do research or propose to do it, evidenced by the number of inquiries we get on this subject. In total these calls are minute compared with those on clinical matters; but, when one weighs the amount of time spent on research throughout the year against the amount of time spent on clinical medicine, it becomes obvious that the index of anxiety is high among researching doctors. It remains nevertheless that my comments are not about hard experience: they are about problems that have been envisaged and feared. They are also comments on how we think those problems ought to be dealt with, and how we would deal with them if they materialized.

This anxiety afflicts the defense societies as well as their members, so we used one minor claim as an occasion to have the matter discussed by the profession. In 1973 the Royal College of Physicians of London called together representatives of the various bodies concerned. The opinions I shall give are roughly the conclusions of that conference.

The first matter is classification according to therapeutic or nontherapeutic experiments. Therapeutic experiments are those where there is at least a hope or intention that the subject might benefit. Nontherapeutic experiments are those where the subject is being used as a "guinea pig."

I argue that therapeutic experiments are no more than the ordinary practice of clinical medicine. The advantage of accepting this view is that patients then know where they are with claims for compensation in therapeutic research because we know where we are in clinical medicine. In clinical medicine, the defense societies will compensate any patient who is damaged through negligence. (The concept of negligence is clear, and all I need add is that disputes about consent come under this heading in British courts.) Failure to obtain valid consent is legally a trespass against the person, which is seldom pleaded as such because it attracts small damages. It appears instead as a negligent act of failing to obtain consent. It is then difficult to rebut the plaintiff's claim to be compensated for the damage resulting from an action not agreed to. Consent may also be imperfect if a patient was not told about possible risks; this may be claimed as negligent.

In addition, there are normal hazards about which all doctors know but which cannot be prevented, such as unavoidable infection, thrombosis, hemorrhage, less than perfect results, and so on. Since they cannot be prevented,

they are not due to negligence. It is just bad luck if such a result occurs, and it has to be accepted as one of the hazards of being ill or being treated. No one pays compensation for such occurrences.

Finally, there are the completely unpredictable complications that have not been described before, or are so rare that no ordinary doctor can be expected to know about them. No one pays compensation for them because it is not possible to anticipate an unknown danger. Unpredictable events are naturally more common with new treatments than with the old. Should they occur often enough to be known, they become matters of negligence if they are preventable, or inevitable hazards if they are not.

In therapeutic research, the question we have to decide is whether it is really so different from clinical medicine that we need a special method to deal with claims. After all, any treatment even as simple as giving an antacid for stomachache is, to some extent, experimental. If we move through treatments where the outcome is increasingly uncertain, we arrive at the extreme of the formal clinical trial. Is it now clear that therapeutic research is something different; and, if so, in what respect is it different? The difference cannot lie in the novelty of the treatment because new methods have always been tried without any suggestion that this takes one outside the field of clinical medicine. It must be because doctors are using special scientific methods to make more than usually certain that their conclusions are valid. I see no reason why this should be allowed to obscure the obvious fact that we are still treating ill patients. As far as claims are concerned, I see no essential difference between therapeutic research and clinical practice.

But there are doubts about this matter. Many doctors who are about to run a clinical trial do believe that there is something different, or fear that there may be, and rightly suspect that the public will be more impressed by the experiment than by the treatment. On these grounds alone they have good reason to inquire. It must also be admitted that what the patient can agree to is different in medical practice than in a clinical trial. The patient should have at least some choice between having a new treatment or sticking to the old in clinical practice. But in the clinical trial this choice is decided by those who run the trial. All that the patient can decide is whether to submit to what the investigator chooses.

In nontherapeutic research the situation is different. There is no possible benefit to be weighed against possible damage; anything that goes wrong is clearly entirely on the debit side. One of the matters on which the college conference was most firm was that any debt to the "guinea pig" must be paid quickly and without argument. The matter was viewed as one of professional ethics because, although doctors in this situation are acting as scientific inquirers, they are still members of a profession that accepts responsibility for those with whom it deals. I am sure there would be a storm of outrage if a

claim were rebutted on grounds such as the fact that the subject had voluntarily accepted the risk. There is also the matter of expediency: the supply of volunteers would rapidly dry up if it were known that compensation is not paid or is difficult to obtain.

I shall now review the sources of damage to see what difference there is between compensation for "guinea pigs" on the one hand and patients and subjects of therapeutic research on the other. The message is that the defense societies will not pay damages in all the cases where they should be received.

Damage from negligence would be compensated by the defense societies in whatever form it occurred. Research work is accepted as a proper activity of doctors. The attitude of the law toward negligence in research is the same as for clinical medicine, and so is that of the defense societies. Here one thinks of inexcusable mistakes, such as injecting potassium intravenously instead of sodium, or cleaning the skin with a corrosive fluid. When we move on to negligence due to failure to obtain valid consent, we are dealing with a matter that is likely to be much more prominent in "guinea pigs" than in patients; it is already a matter of public concern. It is also much more complicated, bedeviled by such questions as whether all "guinea pigs" must be volunteers. And if not, how far can the investigator go? And if so, who, if anyone can give consent on behalf of a person who does not have the capacity because of age or infirmity?

I shall not discuss these matters because it is not my task. But I can point out this still constitutes the matter of valid consent with which we are familiar in clinical medicine, although it is clear that warning of possible risks is much more important with "guinea pigs" than it is with patients. For the defense societies, the question of liability would turn on whether the research worker was negligent in dealing with the situation. If so, we would pay for the consequences.

Next comes the question of normal hazards, such as arterial thrombosis from a catheter. Although these dangers have to be tolerated by patients, there is no reason why "guinea pigs" should put up with them at all because their only prospect of a compensating advantage has been their hope and belief that they may be doing good to humanity. Such altruism may be enough to prevent their making claims, but if not, does the liability fall on the defense societies? The answer is a very firm "no," for it cannot be said that the doctor was negligent when there is nothing to be done to avoid the damage.

There is also the possibility of unpredictable damage. Although we have never had such a claim arising from nontherapeutic research, the sort of hazard I am thinking of is perhaps sufficiently indicated by the troubles that arose from thalidomide or the beta-blocker practolol. If such a claim were made, it is likely that it would come to a defense society in the first instance. I am sure that it would be rebutted because failure to anticipate a danger that was as yet unknown could not be considered negligent.

The defense societies pay compensation only for negligence because the only power the courts have to compel a doctor to pay damages stems from negligence. It is this power that called the defense societies into existence. Virtually all our experience is in clinical medicine so far but we are prepared to do the same for our members in all forms of research and, indeed, could be compelled to do so. We do not and obviously could not operate a no-fault scheme in clinical medicine for all the ills that arise from disease or attempts to cure it, and we are not prepared to make a voluntary exception for research.

Yet no-fault compensation is exactly what we all agree should be paid to "guinea pigs." What is the alternative source?

The meeting at the Royal College took the view that any organization that promoted nontherapeutic research should also accept responsibility for damages, which seems reasonable. The financial burden would be trivial compared with what is spent on research, as is clear from a consideration of how unlikely it is for a claim to arise and from the scale of damages set by the courts. Representatives of research bodies were at the meeting, and they did not disagree with this suggestion. It is difficult for me to say how far it has permeated the large number of organizations that promote research and whether they all agree or would still agree when presented with a claim. But the view of the two largest, the Medical Research Council and the National Health Service, is clear. It is that an *ex gratia* payment would be sympathetically considered, although it is not possible to give a general undertaking. Each group has, in fact, made one payment on this basis.

The scheme is simple enough to understand: those who need compensation get it, and those who have to pay it know their obligations. But I must emphasize that it is notional. We have no experience in therapeutic research, and in nontherapeutic research it is minimal. There will be no accepted routine until enough cases arise that have to be dealt with. Nevertheless I think that the defense societies, which occupy a central position here, will try to push it in the way I have described.

It would be wrong to end on such a satisfied note without saying something about probable causes of dispute. There certainly will be disputes because a graded series of events has been divided into categories, categories create boundaries, and where there are boundaries there can always be argument about which is the right side for a given case. The important boundary here is between negligence and no negligence. The defense societies are used to dealing with this in clinical medicine. But the parties to the dispute will not be the same in therapeutic and nontherapeutic research. In the former the patient is, in effect, claiming from a defense society in the usual way. In nontherapeutic research the "guinea pig" only has to demonstrate damage to get his no-fault compensation. An argument about negligence would then be between a defense society and a research fund; the "guinea pig" should not be brought into it at all. Any argument should be in private and settled quickly lest suspicions

grow that the doctors did not know what they were about or that the prospect of compensation was uncertain.

There could also be arguments about quantum, which are usually settled by bargaining between counsel. If the two sides cannot agree, they go to court for a settlement. In the United Kingdom cases of civil negligence are not tried with a jury. The judge both gives a verdict and decides the sum. Plaintiff's counsel does not name the sum hoped for but is confined to describing the pain and suffering, pointing out how much earnings were lost by an illness, and so on. Such a system is fairly predictable, and it is part of counsel's job to let clients know what a judge might say. This is how damages would be settled for negligence, but I hope that the defense societies would be inclined toward generosity in the case of "guinea pigs." A "guinea pig" damaged without negligence would have no right of action in the courts; again I can only hope that an *ex gratia* payment by a research body would be as ungrudging as we should like it to be.

There is also the possibility that a "guinea pig" might believe that an experiment had made an existing illness worse or caused one to be contracted soon after. This would be a sad affair because the intention to protect and help the "guinea pig" would turn to refusal and even hostility.

After all this speculation I shall now describe the five known cases.

1. Nontherapeutic experiment on a healthy volunteer: The skin of the anticubital fossa was burned by the wrong cleaning solution. Defense society paid on grounds of negligence.
2. Nontherapeutic experiment on a baby: The doctor was doing a series of observations on the capillary circulation of the nail bed. He burned a finger with the heat of the lamp. Defense society paid on grounds of negligence. It is to be noted that these experiments were unlawful because no one in the United Kingdom can give valid consent on behalf of an infant. But this point was not raised.
3. Nontherapeutic experiment on a volunteer patient: Radial artery thrombosed by a catheter. All three defense societies had a member concerned. The work was promoted by a university, and there was no negligence. The Scottish society refused to contribute on principle because it held that the university was responsible. The university was covered by an insurance company that did not share our views on the necessity of prompt compensation for "guinea pigs." The other two societies agreed with the Scottish but decided to pay the damages to stop the argument. This was the case that decided us to ask the Royal College of Physicians to call a meeting.
4. Nontherapeutic experiment on a volunteer patient: Another endarterial catheter thrombosis. Defense society rebutted the claim as there was no negligence. It went further and drew the

research body's attention to the views of the Royal College of Physicians. Nothing more was heard, and I assume that no-fault compensation was paid.

5. A case compensated by the Medical Research Council with no application to a defense society: I have no details, but it was presumably damage sustained in a nontherapeutic experiment.

In conclusion, it seems that things are going according to plan.

As a postscript, I must report on a recent case reported by the Royal Commission on Civil Liability and Compensation for Personal Injury. The commissioners made two comments relevant to my theme:

1. In nontherapeutic research they said: "We think that it is wrong that a person who exposes himself to some risk in the interests of the community should have to rely on *ex gratia* compensation in the event of injury." They accordingly recommended that "guinea pigs" should have a right of action for any damage they suffer.

2. They also recommend that a volunteer in a clinical trial should have a right of compensation from those who organized the trial.

That might do no more than extend the existing practice because drug companies already feel compelled by public opinion to make *ex gratia* payments if there is damage on a grand scale. But from the commissioners' comments it seems to me that they do not recognize the clean distinction between therapeutic and nontherapeutic research and have, therefore, destroyed that boundary. Where is the new boundary to be erected? By implication it is between what is orthodox and what is new. This is ominous, and I can foresee the possibility of the courts inching that boundary away from the formal clinical trial, approaching the point where any doctor treating a patient in a way that has not been done many times before will be liable for damages. Such a trend would have been applauded by the later Pharaohs, but it did fossilize their medicine.

COMPENSATION OF RESEARCH SUBJECTS FOR ADVERSE EFFECTS

Seymour Perry

An HEW Secretary's task force on compensation of injured research subjects has come to the following conclusions:

1. Volunteer subjects in biomedical and behavioral research should be compensated if they are injured in the course of participation in research conducted or supported by HEW. Malpractice or negligence in this context is not a consideration; other mechanisms are available to deal with such injuries.
2. It is not useful, for this purpose, to distinguish between injuries arising in the course of therapeutic or nontherapeutic research.
3. Injuries that should be compensated include "harm, disability, or death, suffered by a subject of research where such injury is:
   a. "proximately caused by such research, and
   b. "on balance exceeds that reasonably associated with illness from which the subject may be suffering and with treatments usually associated with such illnesses at the time the subject began participation in the research." Thus, all normal volunteers would be compensated for injury.
4. Compensation should cover loss of income and medical expenses, but not pain or suffering unless earning capacity is adversely affected.
5. The preferred mechanism of compensation is that of insurance at the institutional level through private carriers, self insurance, or a pool arrangement. Premiums would be chargeable to indirect costs.*

*In June 1977 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research endorsed the recommendations of the task force; in addition, the Commission urged that coverage should be assured "for research which is not Federally funded and for research that is regulated under the Federal Food, Drug, and Cosmetic Act." The Commission also asked that informed consent documents should contain information concerning compensation where such a mechanism exists, or in the absence of such a mechanism, the volunteer would have to bear the cost of any injury. The task force concurred with this latter recommendation.

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The issue of compensation of injured research subjects has been under consideration at various times in the Department of Health, Education, and Welfare for nearly a decade. A number of approaches have been proposed; however, none has been accepted since the social implications are difficult to assess and there were no data upon which to base fiscal estimates.

Volunteers injured in the course of research supported or conducted by the Public Health Service have no legal recourse to seek compensation unless the injury can be traced to negligence or product liability. Through the years there has developed a set of regulations now codified as Part 46 of Title 45 of the Code of Federal Regulations aimed at protecting the rights of individuals and providing for their safety to the extent possible in clinical research. However, even with the best of controls and safeguards, individuals participating in research are injured; and, although the vast majority of medical institutions will provide care for acute injury, it is the exception when long-term care is available to the volunteer who sustains a chronic injury. Furthermore, there is no mechanism to compensate the individual for lost wages or earning capacity. If a volunteer has third-party coverage, his medical expenses may, in part at least, be covered; but generally there is no reimbursement for loss of income.

One notable exception to this situation exists at the University of Washington, which does provide for compensation in the event of research-associated injury. Since 1972 the university has carried insurance for human subjects who are injured in the course of research; insurance is provided by a private carrier with coverage patterned after the workmen's compensation program in the State of Washington. The policy provides compensation covering the actual cost of the medical treatment, of lost wages, and other identifiable expenses connected with unanticipated adverse effects. The policy does not cover children, and volunteers are generally not informed that there is such insurance prior to injury. Approximately 180,000 individuals have been covered from 1972 through 1977 at an annual premium of $35,000. To the present time there have been 15 claims; 14 have been awarded, and no settlement has exceeded $1,500. There is no formal arbitration process, but claims are settled by agreement among the claimant, the investigator, and the insurance carrier.

The issue of compensation began to receive increased attention as concern mounted in the early 1970's over the rights and welfare of volunteers participating in clinical research. That, in turn, led to strengthening informed consent documents and to requirements for establishment of institutional review groups with carefully defined composition and responsibilities. But it took an incident in Boston in 1974 to force action on the part of the Federal Government.

The guardian of a 6-year-old child who was under consideration as a marrow donor for her 10-year-old sibling raised some questions as to the availability of medical care should the donor sustain some unanticipated adverse reaction not attributable to negligence. During court hearings, it was revealed that in the

absence of negligence there existed no provision to compensate either the donor or her parents should an injury occur. Within a short period of time, two additional court cases concerning the same issue occurred. The situation was ultimately settled when the institution involved was able to obtain short-term coverage, with the premiums charged to research grants under which the marrow aspirations were to be performed. It is of interest that the policy that was finally written (and is still in effect) was a no-fault policy with $250,000 coverage per event and with a premium of $100 per volunteer.

This event was a major factor which led the then Assistant Secretary of Health, Theodore Cooper, to urge the then Secretary of HEW, Caspar Weinberger, to authorize a study of the entire issue. Accordingly, in early 1975, the Secretary appointed an HEW task force with the NIH as the lead agency[1]. Law, medicine, and ethics were represented on the task force, which held its first meeting in May 1975 and subsequently held 24 half-day meetings during the succeeding 18 months[2].

The questions confronting the task force were:

1. Should individuals participating as subjects of biomedical research supported or conducted by HEW be compensated for injury arising directly out of such research? Does society, which benefits from such research, have a moral obligation to compensate those injured?
2. If so, which classes of research subjects, therapeutic or non-therapeutic, should be compensated?
3. What types of injury should be compensated?
4. What should the mechanism be for compensation?
5. What process should be followed in compensation?

Specifically, the issues that had to be assessed included:

1. Socioethical and moral obligations of the Federal Government.
2. The legal authority of HEW to require compensation or the assurance of compensation.
3. The incidence of research-related injuries among volunteers.
4. Existing Federal mechanisms for compensation or indemnification.
5. Possible alternative mechanisms for compensation if the task force were to take the position that injured research subjects should be compensated.

To assist the task force in its mission, testimony was solicited from ethicists, clinical investigators, economists, and lawyers knowledgeable in this area; and studies were commissioned dealing with the legal, ethical, economic, and actuarial aspects of the questions and issues confronting the group.

Socioethical and Moral Obligations of the Federal Government

Unquestionably, the key issue concerning the task force was that of the Government's responsibility to provide compensation to volunteers inadvertently injured in the course of their participation in federally supported or conducted research. From the standpoint of fundamental justice and in the context of research, there appear to be three types of justice:

1. Distributive —Both the benefits and burdens of the given activity are distributed over a wide segment of society. This type of justice applies in research whereby individuals in large segments of the population are both subjects and beneficiaries of the research.
2. Reparative —There is an attempt to assign fault in case of injury and then to assess the responsibility of the party at fault to make amends for the injury. This clearly involves deliberate or negligent injury and provides the basis for tort law.
3. Compensatory —Here, amends are made for injury even in the absence of fault or assignment of responsibility for injury.

After extensive discussion and deliberation along with consideration of the opinions of consultants in ethics and law, the task force concluded that society, through the Federal Government, is obliged to make amends for an injury that arises from an activity aimed at benefiting the whole of society. Since society requires and sponsors the research and also is the beneficiary of such research, compensatory justice warrants the redress of injury suffered by persons who are volunteers in such research.

Delineating the limits of the Government's obligation to injured research subjects, particularly those involved in therapeutic research, posed a very difficult issue for the task force. The key question was: Does the volunteer abrogate the right to compensation for injury by virtue of the fact that he has volunteered? Once the task force came to the position that the individual does not lose the right to compensation for injury because of the act of volunteering, it was clear that normal individuals, who do not stand to benefit from the research themselves, should have the right to compensation. On the other hand, an individual volunteering for therapeutic research has an opportunity to benefit personally, which raises a much more complex question. In therapeutic research, it may be difficult to distinguish between the side effects of treatment and the disease process itself, and unavoidable side effects may occur not only in experimental treatments but also in standard therapy.

The task force resolved the issue to its satisfaction by concluding that the distinction between therapeutic and nontherapeutic research is not useful and would greatly complicate the matter. It followed that when injury was proximately caused by research, compensation is clearly indicated. However,

the type of injuries to be compensated presented extraordinarily complex and difficult questions. After several long and vigorous debates, the task force adopted the position that an injury should be compensated if "on balance [it] exceeds that reasonably associated with such illness from which the subject may be suffering, as well as with treatment usually associated with such illness at the time the subject began participation in the research."

Legal Authority of HEW To Require Compensation

Current regulations require grantee and contractor institutions to provide safeguards for the rights and welfare of subjects at risk in research. Properly constituted institutional review groups must be established with responsibility for reviewing research protocols submitted by investigators prior to implementation. Currently, the institution must provide assurance that this process is being followed in all research supported by the Federal Government. An extension of this system, designed to protect human subjects and to provide for inadvertent injury to volunteers participating in research, appears logical and legally acceptable.

Incidence of Research-Related Injuries Among Volunteers

The task force recognized from the beginning that recommendations for compensation would not be acceptable to those who had to make the final decisions. With some uncertainty as to chances of success and apprehension over the effort itself, especially in view of existing concerns over possible malpractice allegations, the task force designed and implemented a trial survey of a small number of clinical investigators. The results of this trial (published in 1977) suggested that investigators would respond candidly and that a larger survey could be undertaken with some confidence. Three hundred and thirty-one investigators were then selected at random from computer files in the NIH Division of Research Grants, reflecting more than 130,000 subjects, including about 40,000 in therapeutic and 93,000 in nontherapeutic research conducted during the previous 3 years. These investigators were sent a survey questionnaire aimed at an assessment of the incidence of both nontherapeutic and therapeutic injuries of various types.

The survey revealed that among the 93,000 individuals who had participated in nontherapeutic research, there were 37 temporary disabilities, 1 permanent disability, and no fatalities. In the 40,000 individuals who had participated in therapeutic research, there were 937 temporary disabilities, 13 permanent disabilities, and 43 fatalities. Thirty-seven of the 43 fatalities were reported to have received chemotherapy for cancer. Further analysis of the data (by Dr. Philippe Cardon, associate director, Clinical Center, NIH) suggested that the risks of nontherapeutic research did not exceed the risks associated

with everyday existence; in therapeutic research, the risks were no greater than treatment in other settings[3].

The task force was cognizant of the problems associated with this survey: the accuracy of reporting was uncertain; individual investigator biases as to what constituted injury could not be assessed, etc. It should also be noted that the incidence of injuries reported in the survey is obviously not equivalent to what might be the incidence of compensable injuries. Nevertheless, the incidence of injuries reported in the survey seemed to confirm the general impression of clinicians on the task force and others that serious injury is not a common occurrence in the course of research on volunteers conducted under existing guidelines and safeguards.

Existing Federal Mechanisms for Compensation or Indemnification

Having concluded that society and the Federal Government have an obligation to compensate individuals for injuries as defined above, the task force proceeded to examine existing Federal mechanisms of compensation. Detailed studies of the Federal Employees Compensation Act (FECA), the Black Lung Act, the Veterans Administration Compensation Act, and the Flood Insurance Program were conducted. In addition, possible legislative mechanisms for compensation and foreign efforts in this area were also examined. No good international model for this country was identified, although in some countries there are mechanisms for compensation that are usually incorporated into a larger scheme of social welfare, national health insurance, and workmen's compensation.

Of the Federal mechanisms assessed, it appeared that FECA provides the most useful model for compensating injured research subjects. It is a no-fault insurance program covering work-related injuries and generally provides compensation for medical expenses, disability, and lost wages. Compensation is not provided for "pain and suffering" as such, unless earning capacity is adversely affected. However, for FECA to be applicable to research subjects, legislative amendments would be required. It should be noted that state workmen's compensation laws do not, in general, provide coverage for research injuries.

Possible Alternative Mechanisms for Providing Compensation

The task force solicited proposals for compensation mechanisms from experts in law, economics, and actuarial science. Each expert was asked to address (1) the factual basis for implementation, (2) potential problems in administration, (3) the nature of the Federal role, (4) additional compensation mechanisms judged suitable, and (5) expected performance of each mechanism during periods of large and small numbers of claims. The task force recognized that different mechanisms might be utilized for research *conducted*

by the Government as opposed to research *sponsored* by the Federal Government. It quickly became obvious that FECA or a newly legislated program would be necessary for research conducted by the Federal Government since other forms of insurance (e.g., private insurance) were not accessible to Federal employees for this purpose.

Insurance mechanisms (other than Federal) suggested by commissioned studies included a private insurance system with Federal underwriting on uninsurable risks and a compensation mechanism created by regulation rather than legislation. Modification of FECA was also suggested to include a deductible coverage under which research institutions would meet certain initial medical expenses and other costs incurred by research injuries.

The task force concluded that the insurance mechanism of choice was private insurance. It presents a number of advantages that make it preferable to insurance schemes that might be put in place by legislation. These include fixing responsibility at the local level, allowing for interaction between the institution and the principal investigator directly, and permitting the development of an insurance "package," of convenient size, perhaps as part of the general liability insurance that all institutions carry. Coverage can be readily extended to non-Federal research in the same institution and to mandated research. The form private insurance might take is flexible, including self-insurance (particularly by large institutions), insurance pools, and coverage provided by insurance carriers.

However, programs requiring legislation, whether modification of FECA or special legislation, would provide an important advantage. FECA is a mechanism already in place, and special legislation has a precedent (i.e., FECA) recognized as working reasonably well. Furthermore, a legislated program would probably be less expensive. However, legislation might require years to enact. It would also be complex; it would need to encompass children and would have implications for other parts of FECA and for other agencies (e.g., the Department of Defense) and would not be applicable to research supported by private sources (e.g., foundations). For research conducted directly by the National Institutes of Health or by the Alcohol, Drug Abuse, and Mental Health Administration, modification of FECA or, alternatively, special legislation would provide the only legal recourse since private insurance cannot legally be utilized by these agencies. It should also be pointed out that the legal basis for requiring compensation in regulated research is not clear. This is an issue that will have to be addressed separately.

The task force recognized that in any case a compensation requirement, regardless of the mechanism, would place an additional burden on research institutions over the substantial legal obligations already imposed on these organizations. However, the sensitivity in American society about the ethics of human experimentation is such that this is an issue that can no longer be ignored. An additional concern arises from the possibility that the availability of compensation would stimulate large numbers of claims, although under the

narrow definition of injury adopted by the task force and based on results of the survey, compensable injuries should be relatively small. Yet, it is possible that the mere availability of compensation may generate large numbers of claims.

Having come to the conclusion that private insurance was the preferred compensation mechanism, the task force began to explore this possibility with the insurance industry. Letters were sent by the Assistant Secretary of Health to 27 insurance carriers and 5 insurance alliances to elicit formal reactions. It soon became obvious that there were two factors that cast uncertainty on the possibility of private insurance: (1) anxiety in the insurance industry over the absence of previous experience in coverage of research subjects (despite the data from the University of Washington), and (2) weakness in the economy, specifically, financial weakness in the insurance industry itself. At the same time, it was also obvious that a federally administered program of compensation, as an alternative, was viewed with some apprehension by the industry. In brief, there was little or no indication of firm interest by insurance carriers in response to the inquiries on behalf of the task force.

The group felt that at this point in its deliberations it had gone as far as it could and that its charge had been fulfilled. However, in view of the remaining uncertainty concerning the mechanism of insurance, the task force recommended to HEW that a "Notice of Proposed Rulemaking" be published in the *Federal Register* to elicit opinions of the research community and to obtain formal reactions from the private insurance industry.

With publication of the task force report, although the recommendations were not to be acted on for some time for a variety of reasons, it appeared obvious to many that societal concerns would inevitably force action if federally supported clinical research is to continue. This prediction seems to have been borne out, and the initial actions aimed at implementing the recommendations are about to be set in motion.

Notes

1. The author wishes to emphasize that much of this presentation is drawn from the deliberations of the task force and from its report.
2. For copies of the report of the task force, "HEW Secretary's Task Force on the Compensation of Injured Research Subjects" and the appendixes, contact: National Institutes of Health, OD/OPPE/DRA, Building 31, Room 1-B-58, Bethesda, Maryland 20205.
3. The survey and the analysis of the data obtained were published: Cardon, P.V., F.W. Dommel, Jr., and R.R. Trumble (1976). Injuries to research subjects, a survey of investigators. N Eng J Med 295:650-654.

DISCUSSION

F. William Dommel

The presentations by Dr. Harman and Dr. Perry provoked an active discussion that focused primarily on the following issues:

A question was raised as to the appropriateness of not informing subjects of research as to the availability of a no-fault compensation mechanism in the event of a research-related injury. Most agreed that prospective subjects of research should be so apprised. A case in point is that at least one Institute within NIH has been advised by one of its review bodies that in the future they will insist on proof of such notification. It was also remarked that *The Health, Education, and Welfare Secretary's Task Force on the Compensation of Injured Research Subjects*, of which Dr. Perry was the chairman, also recommended such notification.

The difficulty in distinguishing between therapeutic and nontherapeutic research procedures was discussed. It was argued that in light of this difficulty a compensation mechanism that would afford benefits only to those injured by therapeutic procedures would incur serious definitional problems. A minority view, however, was that even though the two categories (therapeutic and nontherapeutic) do indeed merge, there is in practice a clearly identifiable distinction between them when judged by the physician-researcher.

A further question discussed was: Should the availability of compensation in the event of injury be influenced if a research subject is paid for his participation? It was generally agreed that compensation should not be dependent on whether there had been payment to a volunteer. It was mentioned that the payment of volunteers for their participation in research does raise an ethical issue in itself under most circumstances.

The Royal Commission report concerning compensation for research-related injuries (about which Dr. Harman spoke) was a further discussion topic. He mentioned that this particular report only speaks to product liability and does not address the topic of medical service injuries in research. Some agreed that it would seem proper that compensation for injuries occurring in the course of testing new drugs should be provided by the drug manufacturer, as the Royal Commission recommended. However, contrary to the Royal Commission's recommendations, it was suggested that the drug manufacturer should not be responsible for medical treatment injuries occurring in the course of additional testing (not conducted by the manufacturer) of an already licensed drug. Some thought that it may have been a mistake that the Royal Commission made no provision for compensating medical service injuries in research. Noting the fact that malpractice insurance fees and the number of malpractice claims have been rising at a high rate, some felt it likely that claims

against researchers might follow the same course once it is known that compensation is available. There was some agreement with this point, but generally it was felt that we really will not know the answer until a compensation program can be enacted and the results reviewed. Dr. Perry mentioned that the compensation program recommended by the HEW secretary's task force studying compensation would be a no-fault program and would not require adjudication in the courts. The task force expected only a small number of valid claims once the mechanism was in place. Dr. Perry noted further that there had been some experience with the operation of a compensation mechanism at the University of Washington and that very few claims had been made during the more than 5 years of the program. The university's experience, however, cannot be used to predict assuredly the number of claims that might arise elsewhere since the volunteers were not advised that compensation might be provided if they were injured in the course of the research program.

Dr. Harman was asked if nonmedical (nonphysician) personnel were eligible for membership in the defense society in the United Kingdom and through this membership to be insured against injuries judgments. Dr. Harman said that to the best of his knowledge nonmedical persons were eligible and would need only to apply for membership.

One commentator expressed his concern about the lack of available insurance for research injury in the United States today. He noted that he had been unsuccessful in seeking such coverage and, in fact, had found only one carrier that was insuring one large-scale clinical trial in only one city in the United States. In the search Lloyd's of London agreed to provide such coverage, but the cost would have been prohibitive. At this point, Dr. Perry noted that in late 1976 the Assistant Secretary for Health, HEW, at the request of the task force, had contacted 27 insurance carriers and 5 insurance alliances seeking no-fault insurance coverage for injuries in HEW-supported research. Nine carriers had no interest, nine were slightly interested, and nine wanted to study it further. However, institutions with other insurance companies might be more successful in their contacts with them. The University of Washington no-fault insurance compensation coverage has been a moneymaker for the Aetna Life and Casualty Company.

The discussion centered once again on the kind of research that should offer compensation to those who are injured while participating. It was expressed that there is a great similarity between therapeutic and nontherapeutic research, in that the subject is serving society and his or her own benefit is not the *only* consideration of a therapeutic subject's physician, as would be the case outside the research setting. This suggests perhaps that both therapeutic and nontherapeutic research should offer compensation to those who incur injuries while participating. A minority argument contrary to this point was expressed when it was noted that all medical practice produces benefits from learning. Thus, research medicine is not unique in providing new information.

In continuing the discussion of the kinds of research that should have a compensation mechanism in place, one physician expressed the concern that to draw a line between therapeutic and nontherapeutic research is much more difficult than one might suppose. He suggested that if he had a patient with a duodenal ulcer and, with his permission, tested a drug more powerful than was necessary for his condition, this would be therapeutic research. Yet, if the subject were injured by a drug more powerful than his condition warranted, it would only be fair to compensate him for such an injury. As this stimulating conversation drew to a close, Dr. Ryan, chairman of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, explained that this Commission had abandoned the use of the terms therapeutic and nontherapeutic in referring to research in general and had adopted in place the term therapeutic *procedure* and nontherapeutic *procedure* for specific treatments or tests. Time restricted further discussion.

Part 5

CLINICAL RESEARCH ON CHILDREN

Robert E. Cooke

There is a unique importance to research on infants and children; yet they represent the group least able to consent, assent, or object meaningfully. Questions, therefore, arise as to the ethical justification for such research. Considerations include: proxy permission in lieu of consent; the concept of the family as a partially autonomous unit requiring respect but also possessing obligations; the question of for whose benefit—child or caretaker—research permission is granted; and the concepts of graded autonomy and graded childhood. Each of these considerations lends some justification to the practice of research with infants and children.

The National Commission for the Protection of Subjects of Biomedical and Behavioral Research has completed and released its report, *Research Involving Children*. Prior to that report it had considered research on the fetus, research involving prisoners, ethical principles underlying research, and psychosurgery. Without question the Commission had more difficulty in arriving at its recommendations in regard to children than in any of the other charges given it by Congress. There seemed to be more areas for difference than in all the previous deliberations. I am personally less satisfied with our conclusions in this case than in our other reports.

S. Hauerwas, in his paper to the Commission on Ethical Issues in the Use of Human Subjects, affirms this belief.

> The ethical issues raised by the use of prisoners and the poor seem simple when compared to the problems involved in the use of children and other non-competents. In order to develop certain kinds of drugs or procedures we can do all the animal and adult testing we want and still we must finally test on children—i.e., a test group who by definition cannot give informed consent. Paul Ramsey has argued that no one, parent or guardian, even with the best intentions has the moral status to consent for a child to be made the subject of medical investigation solely for the accumulation of knowledge (except when epidemic conditions prevail). To quote: "Where there is no possible relation to the child's recovery,

> a child is not to be made a mere object in medical experimentation for the good to come." If it is objected that this severely restricts possible advances in childhood medicine, Ramsey argues that the moral progress of the race is more important than the scientific. Thus, testing of children is the paradigm instance that at times it may be necessary to choose between morality and knowledge even though we normally assume that we do not have to choose between them [1].

Five areas seem to me to be of particular significance.

1. The ethical justification for research involving infants in contrast to others in our society—namely the survival imperative.
2. Proxy permission in lieu of consent.
3. The family as a partially autonomous unit requiring respect and possessing obligations.
4. The question of benefit for whom—child or caretaker.
5. Graded autonomy and graded childhood.

These issues consumed much time and energy and were resolved only partially despite much discussion. The practical significance of the first three, at least, can be appreciated somewhat from the following personal research experience, which dramatizes but does not exaggerate the problems.

Heat Stress on Infants Study

In 1948 two associates and I were concerned with the effects of heat stress on young infants. The reasons for that interest were that a large number of infants live under circumstances in which there is significant heat stress, that evidence from studies in adults might not be applicable to infants, and that there was no information available as to what feeding mixtures were appropriate and what water intakes were proper under such circumstances. We carried out extensive balance studies on a series of infants—4 weeks to 6 months of age—in a controlled environment comparable with hot summer temperatures. Changes in body water and electrolyte that occurred over a number of days were calculated from precise measurements of intake and output, including skin washings, blood chemistries, and body weight. The infants, all black, came from an orphanage in which personal attention was extremely limited because of inadequate financial support. During these studies the infants received far better attention from our round-the-clock "foster mothers" (nurses) than they had in the orphanage. In our minds the improved care compensated for the fact that we had to draw blood from these babies using techniques that were not without pain or risk. These infants were also subjected to the additional discomfort of being restrained for the purpose of

collecting urine and stools for a number of days in an unpleasantly warm environment. At the end of the study the infants did have the great advantage, compared with other infants from that orphanage, of being placed in foster homes.

Retrospectively, my guess is that in the long run those infants were probably not harmed and may actually have had benefits by virtue of their unconsented participation. On the other hand, looking at these experiments from my present perspective and that of existing institutional review boards, or from the standpoint of the Commission's recent report, I would conclude that those experiments could not be done at the present time for many reasons, including discrimination in the selection of subjects. Yet, was the work worthwhile?

The balance studies showed remarkable retention of sodium during heat stress, which produced rather serious intracellular dehydration (despite weight gain) leading to significant illness and fever. As a consequence of those experiments there was a major change in the feeding practices for infants throughout the world, with a substantial decrease in morbidity and mortality everywhere.

Justifying Research With Young Infants

This experience illustrates the particular problem of ethical justification of research with children. The human infant, because of the extreme immaturity of the species at birth, requires many interventions to survive, compared with the adult. What interventions are necessary, when should they be made, how much must be established to prevent serious harm to substantial numbers of normal individuals? The premature infant, for example, is not an abnormal part of our species but a human being in the early stage of life. Such normal individuals will be seriously damaged or die in large numbers unless interventions are appropriate. The central nervous system is immature, as are the respiratory, gastrointestinal, and urogenital systems. Adaptability is so limited that if the interventions are not tuned very finely, there is no survival. We are not talking about having people lead happier and nicer lives, we are talking about survival. That fact introduces into the area of infant and child research a new imperative—not a scientific imperative that we must have more knowledge—but a survival imperative. If interventions are not appropriate, large numbers of individuals die or are seriously damaged.

If oxygen is not administered to immature infants, many deaths occur. If too much is given, blindness results. If chloramphenicol to prevent sepsis is given to prevent babies from dying of infection, the death rate increases from the "gray baby syndrome." A drug such as Gantrisin, which is well-tolerated by adults, produces kernicterus, severe athetosis, and cerebral palsy. Yet the answer is not simply going back to the old way. We know, for example, that for a substantial number of babies in some parts of the world breast milk is inadequate as a feeding mixture and that infants will not develop and thrive.

Thus a serious problem exists in regard to research in infants and young children, who cannot ever give responsible consent. If interventions are inappropriate, there is no benefit; but there also can be very serious harm. Giving too much water to a baby can produce serious damage. Too little water can produce damage also. Those of you as old as I may remember the days when premature infants were not fed for 3 to 4 days so they would not die from aspiration. Cerebral palsy and death were probable consequences of the hypernatric dehydration that some suffered.

How do we ascertain such consequences? Do we rely on trial and error, as with the use of oxygen, where literally thousands of babies were blinded? Or do we carry out research? Do we learn something about normal human development so we can anticipate problems and avoid a rise in infant mortality as a consequence of the use of a drug such as chloramphenicol? I conclude that research in infancy is necessary to prevent widespread harm. In contrast, an absence of research later in life—although depriving us of significant benefits—would not result in a great amount of harm.

The prohibition of research such as described, if proposed to be carried out on normal healthy white infants of upper-class educated parents, would certainly be explained in terms of the limitations of proxy permission or consent.

> No parent has a legal right to give consent for the involvement of his child unless for the benefit of that child [2].

No one has the right to volunteer another for someone else's benefit.

What Is Consent?

If research on infants and children is so necessary, are there ways that it can be ethically justified in the absence of consent by the subject?

To answer that question it is necessary to look at what consent represents. Why is consent important from an ethical perspective? Most people agree now that, even though no risk or harm is involved, except for observational activities in public places consent of someone is necessary if you are doing something with that individual. That means that consent is important for more than the protection of the individual from physical, mental, social, or economic harm. Further, most people agree that consent might provide some protection, but it is clear that such protection is limited. Persons are frequently coerced unknowingly. For example, a patient who has a 100 percent fatal disease cannot easily resist the trial of a new therapeutic measure. He or she is going to die without it—and might live with it. There is obviously not very much freedom of choice in that situation, but there is a great deal of subtle coercion. Even more subtle than that is the physician relationship with the patient. The patient respects the doctor; the patient is somewhat indebted to the doctor.

If one reads consent forms carefully, in the cancer chemotherapy area, for example, one would have to be a good clinical pharmacologist to understand what is meant. Indeed the institutional review board preliminary report to our Commission indicated that the reading level of most consent forms is about 3d- or 4th-year college level. The comprehensibility was at a very high level, and the comprehensiveness was at a relatively low level. Thus in the consent process, people can give responsible but uninformed consent. Consent is poor protection. Institutional review boards can provide far better protection against physical or mental harm than consent. Yet consent is said to be important for two other reasons: respect for the autonomy of the individual and respect for the dignity of the individual. Even though there is no risk, we expect consent out of respect for the freedom of the individual to choose, and out of respect for the person as an individual.

How then do these aspects of consent apply to the infant or young child?

Consent and Autonomy

Autonomy means freedom to choose—the ability to determine one's own course of life. However, such a concept is meaningless when applied to the infant. Consent to recognize autonomy when autonomy is not present is nonsense.

Consent out of respect for the dignity of something or someone does not have to be given by the individual. For example, we do not allow a cadaver to be mutilated. Before one can do an autopsy, permission from a caring person must be obtained. We have certain respect for dignity also. We do not allow people to desecrate a mountain; we require some acceptance by the community. The consent to recognize dignity does not have to be given by the mountain. The experiments that were rather horrifying to the Commission in which a dead fetus was decapitated and perfused to study brain metabolism lacked respect for the dignity of the fetus, even though people might have agreed to abortion. Decapitation of a fetal dog and perfusion would probably not generate that kind of revulsion. Consent, then, can be given to recognize the dignity of other individuals.

Family Consent

How do we justify carrying out research in the individual when it is not for his benefit? Richard McCormick takes the position that one can make the presumption of what an individual ought to do. Natural law doctrine indicates that individuals owe something to other members of the human species; they have an obligation to assist. If one makes a presumption of what a child would wish, the child would not only wish to do this but ought to do this. Unfortunately, I cannot agree with that approach in its application. If applied, one should be able to draft adults for nonbeneficial research because adults ought

to assist. No one is recommending the drafting of adults as research subjects; therefore, no one should draft infants. That is simple justice.

Hauerwas looks at the problem from a perspective similar to mine. He does not assume what a child ought to do but what a child *is* or *is not*. He agrees with what every pediatric researcher would agree with—namely, that a child is *not* a small adult—morally as well as physiologically. He further asserts that the child must be viewed as an integral part of a family—a "natural" in Aristotelean terms, not a contractual institution of society.

> We do not ask to be born into families, we simply are born into families of one kind or another. In a decisive sense the family is not a voluntary institution and the kind of responsibilities that accrue in it are thus different. Morally children are not simply smaller, younger, dependent, and less "rational" than adults. Morally the meaning of "child" is relative to the interests and needs of the community as mediated through the family.
>
> In other words, to speak of family and child is exactly to speak of duties of parents and children toward one another that are grounded in the concrete expectations of particular communities.
>
> The argument is not one of rights of children but rather one of responsibilities to them irrespective of their ability to make claims upon us. It is not one of personhood. We care for children because they are children, not because they are persons [3].

Trust, love, and care for the child are integral parts of a family. The obtaining of consent by the family for actions toward that child is out of respect for *these bonds*, not out of respect for the child as an autonomous being. Proxy consent can be seen equally as an attempt to protect the integrity of the family unit.

It is true that parents may not always know what is best for their children. The important issue is that the historical tradition of family expects that the family *should*. "In other words proxy consent (or permission) as an institution (or procedure) is one way to insure that whatever is done to the child is done in accordance with the moral conventions and traditions of that family." [3].

My position comes very close to that of Hauerwas. Infants and children are part of families, and of the human race. They are not to be excluded automatically from research because they cannot make decisions on their own behalf—because they cannot give consent. If the family participates in research, if the family heads—the parents—give permission or consent to participate, the younger members can be enrolled, I argue, even though they cannot comprehend or possibly even object.

Permission on behalf of the infant to participate alone is considerably different from consent on the part of the family as a unit to become involved. The family as a unit is recognized by society as having considerable freedom to

choose what is best for itself. What I propose is essentially that research related to members of a family is acceptable providing there is family consent for participation of the family.

What does that mean? It means that the family is enrolled, the parents as well as the child and infant, providing both parents agree; providing the family continues to participate in the studies, that some senior representative of the family is present when there are procedures carried out; and providing they are there as participants to withdraw from the experiments whenever the activities are uncomfortable to the family. Consent of the parents to participate, essentially family consent, recognizes the freedom of families to choose, but it must be a unanimous choice. Thus, in research of a nonbeneficial type both parents must agree; the family must be participants, not simply the infant, and the family is there to withdraw if procedures are painful. The parent can judge and the family and infant can withdraw. This is not proxy consent for another individual; it is consent for family participation.

That kind of consent exists in sociological research. The chief or the senior members of a tribe can consent for the tribe. The heads of organizations/associations can consent for the members, providing you are not harming individual members.

What kind of safeguards do we require if we recognize that the family can provide consent for participation of the family? First, both parents must consent (a one-parent family may not be the most desirable type to enlist). If there is no family, as in the case of orphan babies, research could not be done unless they could benefit immediately, because these individuals are not representative members of a family.

Nontherapeutic research on infants is acceptable under such an approach providing (1) animals, adults, or older children who are consenting, mature minors have been studied previously when feasible; (2) no alternative means are available; (3) the sought-after information is highly valuable to prevent harm and do good; (4) every effort is made to utilize procedures being carried out as part of usual medical and nursing care; (5) the least invasive and the least uncomfortable procedures possible are utilized; (6) the risk is no more than minimal; (7) there is no unfair discrimination in the selection of subjects; and (8) there is careful scrutiny of the motivations of the family that volunteers to participate to ensure thoughtful family consent.

Those familiar with the report of the Commission know that, in general, the Commission did not accept this proposed solution; instead it permitted proxy permission for procedures, approaches, or experiments that did not offer immediate benefit to the individual, providing the risk was only a minor increase above minimal. It suggested but did not require participation of the family and thereby acknowledged the validity of proxy consent or "permission."

The definition of minimal risk was kept so restrictive, however, that it could be considered no additional risk beyond that of everyday living. My objection to the minor increase above minimal rests with the indefiniteness of "minor"

and the likelihood of wide ranges of interpretation of that standard. Admittedly minimal as the limit of risk is vague, but the additional vagary, minor, compounds rather than clarifies the situation.

When interventions are carried out as a part of research that might benefit the child, few physicians, lawyers, or ethicians raise concerns. Permission is granted by the parents or other caretakers with the obvious expectation that all "therapeutic" approaches are directed toward the best interests of the child. Unfortunately, that might not always be the case.

In the application of rules related to the conduct of research or, for that matter, the provision of services, it is important yet difficult to distinguish always between research on behalf of the caretaker and research on behalf of the individual child.

In the study of a group of patients who are hyperactive, are amphetamines given to the child for the benefit of the child, or his teacher, or his parents? Certainly, improved behavior makes life far easier for the teacher and the parents. Yet if the child is appreciated more by his caretakers and his performance is improved, is he not benefited? It is not an easy distinction. A number of years ago in Cleveland carotid-jugular anastomosis was developed to revascularize the brain of children with Down's syndrome so that through retrograde flow there would be a greater volume of blood going to the brain. Was that for the benefit of the parents or for the child? It turned out to be of no benefit, but it certainly was a procedure that could be questioned. Gastrostomy to assist feeding of the severely defective was a common practice in the Sunland Training School in Florida until a short while ago. A tube is inserted, feeding time is shortened, and the budget is reduced in that institution. Such actions were for the benefit of the caretakers, certainly not the child.

As far as therapeutic research is concerned, the child who is not able to consent should not be in the forefront of research. When feasible, where survival of that individual is not at stake, research should be carried out on adults or consenting older children prior to therapeutic research in the younger group. Every effort should also be made to plan therapeutic research to conform as much to the treatment routines as possible, generating as little discomfort and as little risk as possible.

Autonomy From Family

When experimental subjects are beyond infancy and early childhood but are not adults, some responsibility for decision-making may be given to the subjects regarding participation in research, whether classified as therapeutic or nontherapeutic. However, attempts to translate the principle of graded autonomy or graded responsibility for making one's own choices into specifics have not been particularly successful. In principle, if one follows Hauerwas's reasoning regarding the child's place in the family as an element of consent by the family for the child, the degree of emergence of the child from the family

confines is a rough index of the extent of decision-making to be allowed by that child. Participation in school is one mark of such partial emergence from the family, and some assent or dissent could be recognized if given by the schoolboy or schoolgirl. Likewise, independent living outside the family could certainly be recognized as an indicator of the adulthood of the individual. With children between these two limits, approximations must be made based not only on the degree of independence permitted by the family but also on the seriousness and complexity of the problem. Dissent should certainly be recognized if no benefit will accrue—but not if death or serious disability would be the alternative to participation in research aimed to benefit the individual.

Conclusion

I have argued for the unique importance of research especially concerned with young children, even though that is the group least able to consent, assent, or object in a meaningful way. I have argued for participation of the family in recognition of the importance of that unit in society and as a protection for the child's well-being and dignity. The ethical bases for these arguments have been presented only sketchily, and it is hoped they will be developed in years to come as the debate continues.

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CLINICAL RESEARCH WITH CHILDREN

June K. Lloyd

Clinical research is necessary at all ages during childhood so advances in medical knowledge can be made and used to benefit children. The statement of the Medical Research Council of the United Kingdom (1963) provided for research connected with the management of the individual child, and intended for the benefit of that child, to be conducted with the consent of the parents if the child was not old enough to give consent himself. Similar considerations were held to apply to preventive research procedures, such as the development of vaccines. For nontherapeutic research, however, it was considered that children under 12 in the United Kingdom could not give consent to a procedure not of direct benefit and which could carry some risk of harm; furthermore, parents could not legally give their consent to such procedures. Nevertheless nontherapeutic investigations are carried out with parental permission, and virtually all research investigations involving children (therapeutic and nontherapeutic) are submitted to local research ethical committees for approval. The previous opinion of the Medical Research Council regarding the nonlegality of parental consent is being challenged in the medical press but has not been tested in the courts. In many respects, current United Kingdom practice conforms with the U.S. recommendations, but the role of research ethical committees is less clearly defined. There is also no provision for a national advisory committee.

The Rights of Children To Be Involved in Research

The U.S. Commission [1] summarizes the arguments in favor of conducting research in children with two points: the lack of an alternative population, and the consequences of not involving children in research. The rights of children to share in the benefits of advances in medical knowledge and, equally, to be protected from the harmful effects of applying knowledge gained only by studies on animals or adults cannot be overstated. Children are not scaled-down adults in terms of growth or development; neither are they a homogeneous group in terms of their growth rate and the maturation of developmental processes throughout the childhood years. Thus, research is needed across the whole range of childhood. Just as it may be inappropriate to use the results of studies gained in mature adults for planning regimens in children, so knowledge acquired about older children could be inapplicable in the newborn period. Numerous examples can be given of conditions that are unique to the childhood years and have no other mammalian model; these include many of the

congenital malformations and inborn errors of metabolism, as well as some of the behavioral disturbances. Likewise, the physiological and psychological differences between children of different ages, and between children and adults, are becoming better understood, with improvement in such areas as the management of fluid and electrolyte disturbances and drug therapy and with changes in many of our clinical practices, such as the rooming-in of parents with their children in the hospital. The consequences of not involving children in research are far reaching; not only would the development of improvements in treatment for diseases in childhood be restricted, but also the evaluation of new therapies (initially worked out perhaps in animals or adults) would be hampered. Furthermore, research into diseases of adult life that have their origins in childhood would be adversely affected.

To those involved in the care of children, and to those in clinical research in this age group, the needs of children to have research done and their rights in this respect seem so self-evident that it is sometimes assumed that the principles are widely accepted. It could, however, be dangerous to rely on this assumption. Many in our society are concerned about research in children, but not all are conversant with the needs for research or convinced of the rights of children to participate in research procedures. Certainly in the United Kingdom it is necessary to spell out the arguments, as has been done by the U.S. Commission. It is encouraging to note that the first recommendation of the Commission specifically states that "research involving children is important for the health and well being of all children . . . [it] can be conducted in an ethical manner . . . and should be conducted and supported." Such a positive approach is clearly both welcome and necessary.

Therapeutic Research

Therapeutic research on children is designed to hold out hope for benefit of the child involved. The Medical Research Council in the United Kingdom in a review on Responsibility in Investigations on Human Subjects [2] stated that "in the case of procedures directly connected with the management of the condition in the particular individual, the relationship is essentially that between doctor and patient," and it considered that to "obtain the patient's agreement before using a novel procedure is no more than a requirement of good medical practice." In relation to children the statement continued "that it is clearly within the competence of a parent or guardian of a child to give permission for procedures intended to benefit that child when he is not old or intelligent enough to be able himself to give valid consent." I shall return later to discuss views in the United Kingdom regarding the age at which children can be considered to be able to give valid consent, but the implications of this statement would be in general agreement with recommendation 4 of the U.S. Commission. Both countries seem to agree that this type of therapeutic re-

search is necessary and can be conducted, and that it is perfectly valid for parents to give permission on behalf of their children.

It must be accepted that the results of therapeutic research might be, and often are, of greater benefit to future children who have the disease in question than to the individual participating in the research program, but this does not invalidate the principle. In my experience parents will often spontaneously say that they are glad to know that studies in which their child is participating will help other children. Perhaps the most obvious examples of this type of research are the clinical trials of cancer therapy in children. The *Archives of Disease in Childhood* contains a report of the multicenter trial organized by the Medical Research Council of the management of nephroblastoma in childhood comparing two forms of maintenance chemotherapy [3]. Although the group of children assigned to one type of therapy did less well, the survival in both groups was better than had been previously obtained by the uncontrolled therapy of individual patients; no one would seriously question the ethics of this kind of research. It is also important to note that the trial was stopped as soon as results from a different trial in the United States indicated that therapy using a combination of drugs was superior to that using any single drug.

The extent to which parents (and children if they are old enough) should participate in decision-making in therapeutic trials could perhaps be debated. Where two treatment regimens are being compared, how far is it necessary, or even desirable, to burden patients with a discussion of what might be complex technical problems? If their child is receiving treatment that is currently accepted and could be used without question by any medical practitioner, do parents need to know that their child is participating in a trial of this treatment? My own view, which I think would be shared by many colleagues, is that parents should always be fully informed. The recommendations of the U.S. Commission place the major responsibility for ascertaining that the research is appropriate, properly conducted, and that parental permission has been obtained on institutional review boards; the U.K. counterpart is the research ethical committee. Current U.K. practice, however, would be that all research programs involving children, whether for therapeutic benefit or not, should be considered by such a committee; and most grant-giving bodies demand a statement that the plan of the investigation has been so approved.

Preventive Research

Research into methods of preventing disease in individuals has tended to be considered as therapeutic research. There are, however, some obvious differences. Children on whom research intended to prevent a disease is carried out are usually healthy at the time of the procedure and might have never contracted that disease; if they suffer as a result of the preventive measure, the problem is of a somewhat different order than that of complications occurring during trials of measures to alleviate a condition from which they are already

suffering. Furthermore much preventive research is actually aimed at protecting the community and children in general. For these reasons I propose to consider briefly this type of research as a separate entity.

The major example of preventive research is probably the development of vaccines for the protection of both individual children and of the community against infections that have their major impact in childhood. Appropriate clinical trials of such vaccines can, in most cases, be carried out only in children, and often only in young children. The Medical Research Council [2] considered that the ethical and legal considerations for trials of preventive measures, such as vaccines, were "the same as those that govern the introduction of a new treatment." On this basis various trials of immunizing procedures have been carried out, the fourth and the latest report of the Medical Research Council's trials of measles vaccines having been published [4]. The results show benefit to the children, who have had a high level of protection lasting now for over 12 years without any untoward complications; there has been benefit also for the community, with a reduction in the incidence of measles. No one has any qualms about this piece of research.

The situation regarding immunizing procedures against pertussis is, however, less happy. The first clinical trial by the Medical Research Council [5] was inconclusive, and further trials were conducted [5,6]. Mass immunization was introduced; but continued doubts about its efficacy, and more recently fears about its safety, have persisted. Even though both retrospective and prospective investigations of the relationship between pertussis vaccination and encephalopathy are still proceeding; the U.K. Government has already agreed [7] that children suffering severe ill effects as a consequence of a public health policy would be eligible for compensation. The Parliamentary Commissioner for Administration has, in fact, criticized the Department of Health for not having sufficiently warned parents about the adverse reactions against the vaccine [8]. The present situation is that the proportion of children immunized fell to 39 percent in 1976, compared with about 80 percent in 1974 [9], and the number of cases of whooping cough in 1977 was 2 to 3 times that in 1976. The Department of Health is now proceeding with a publicity campaign to encourage immunization, but the prospective study regarding the complications of immunization is not complete and may founder because of the low takeup of the procedure.

What would be the ethical constraints of setting up a further trial in this situation? I do not think the Medical Research Council statement gives enough guidance. A disease is not being treated; it is only possibly being prevented, and the risks of the procedure might not be minimal. Nevertheless the problem is an important one for the general health and welfare of children. As far as I understand it, the recommendation of the U.S. Commission that would be appropriate for such a study is number 6, which provides for additional approval by a National Ethical Advisory Board, for public review and comment,

and for subsequent assent by the secretary of the responsible Federal department.

As more emphasis is being placed on prevention I believe that we shall need to consider in more detail how research is to be conducted in this area, and it may be that the coordinating role of the Medical Research Council in the United Kingdom will need to be strengthened by a national body along the lines proposed for the United States.

Nontherapeutic Research

The Medical Research Council [3] stated that for adults nontherapeutic investigations may only be done if "consent is freely given [by the subject] with proper understanding of the nature and consequences of what is proposed," and such consent should be obtained in writing in the presence of another person so evidence is available that a proper explanation has been given, understood, and accepted.

In relation to investigations on children, the Medical Research Council made the following recommendations and, as these remain the main official guide under which research ethical committees operate, I will quote them in full:

> In the strict view of the law parents and guardians of minors cannot give consent on their behalf to any procedures which are of no particular benefit to them and which may carry some risk of harm. Whilst English law does not fix any arbitrary age in this context it may safely be assumed that the Courts will not regard a child of 12 years or under (or 14 years or under for boys in Scotland) as having the capacity to consent to any procedure which may involve him in injury. Above this age the reality of any purported consent which may have been obtained is a question of fact, and as with an adult the evidence would, if necessary, have to show that irrespective of age the person concerned fully understood the implications to himself of the procedures to which he was consenting. Even when true consent has been given by a minor or a mentally subnormal or mentally disordered person, considerations of ethics and prudence still require that, if possible, the assent of parents or guardians or relatives, as the case may be, should be obtained.
>
> Investigations that are of no direct benefit to the individual require, therefore, that his true consent to them shall be explicitly obtained. After adequate explanation, the consent of an adult of sound mind and understanding can be relied upon to be true consent. In the case of children and young persons the question whether purported consent was true consent would in each case

> depend upon facts such as the age, intelligence, situation, and character of the subject, and the nature of the investigation. When the subject is below the age of 12 years, information requiring the performance of any procedure involving his body would need to be obtained incidentally to and without altering the nature of the procedure intended for his individual benefit.

Although this statement does not, as Curran and Beecher [10] have noted, outlaw all clinical investigations on all children where there is no direct benefit to them, it would certainly appear to make investigation on babies or young children virtually impossible. However, the Medical Research Council's advice rested on the opinion of a single lawyer and, although the legal division of the Department of Health and Social Security gave essentially similar advice, the proposals have never been tested in the courts. Many nontherapeutic investigations have been, and are being, conducted on young children in the United Kingdom with parental permission and with the approval of research ethical committees. In most respects the recommendations of the U.S. Commission are already being fulfilled, but there are some important differences.

Function of Research Ethical Committees

Research ethical committees (REC) are the United Kingdom's counterpart of institutional review boards but are not set up or controlled by any central government agency. They were established by hospitals on the recommendation of the Royal College of Physicians of London [11], who outlined the following functions:

1. An REC should be a small committee set up solely to supervise the ethics of clinical research.
2. The medical members should be experienced clinicians with knowledge and experience of clinical research.
3. The REC should have a lay member.
4. To remove any uncertainty about which procedures should be submitted to an REC, all proposed research investigations on human beings should be submitted.
5. Whenever a research investigation is not expected or intended to benefit the individual patient, a full explanation should be given. The patient should be free to decline, participate, or withdraw at any stage.
6. Whenever possible the consent of a patient should be obtained in the presence of a witness.
7. When there are circumstances in which it is genuinely inappropriate to inform a patient fully, the REC should examine the situation with special care.

8. Particular care is needed if a clinical investigation is proposed in children or mentally handicapped adults who cannot give informed consent. The parents or guardians should be consulted.
9. Particular care is needed if a clinical investigation is proposed on a subject or patient who has any sort of dependent relationship to the investigator, e.g., student, laboratory technician, or employee.

Because the Medical Research Council and most other grant-aiding bodies will not give financial assistance unless an investigation is approved by an REC, and because reputable journals will not publish the results of research for which ethical approval has not been obtained, virtually all hospitals and other institutions where research is conducted have REC's. Their composition, however, varies. Except for those in specialized children's hospitals, it is likely that the members have little knowledge of the problems and needs of research investigations with children. Lack of official guidelines as to the conduct of research with children also leads to uneven decisions, and the establishment of more effective ethical committees for consideration of research in children must be a priority in the United Kingdom.

Age of Consent

The age at which a child might be expected to understand a procedure and give or withhold his consent has not been defined. As the exact age is in any case bound to vary from child to child this is probably wise, but the implications of the Medical Research Council's statement are that in England children ages 12 years or under would be regarded by the courts as being incapable of giving consent. This view has never been tested in the courts, and a recent legal opinion [12] has stated that children of any age who can understand and decide about what is involved in a nontherapeutic experimental procedure can legally give consent. The U.S. Commission prefers to use the term assent rather than consent and states that such assent will normally be required for children who are 7 years or older, although parental permission is also needed. Dr. Cooke has cogently argued that the autonomous unit is the family and that, when viewed in this light, the family gives consent. The exact role of the child or parent, therefore, requires less precise definition.

Risk of Procedure

In nontherapeutic research it is assumed that the risk of the procedure must be minimal, or at least small. Risk has not been defined in any U.K. guidelines. The Medical Research Council talks about procedures that "may carry some risk of harm." Value judgments, therefore, have to be made by investigators, ethical committees, and parents. The recent experiences [13] of an investigator

who wished to obtain blood samples from infants have been the subject of a brisk correspondence in the British medical press (*Lancet*). Whereas the U.S. Commission includes obtaining blood specimens as a procedure that would cause minimal risk, the view of an REC in the United Kingdom was that blood sampling for research in infants was not legally permissible. This view was generated in part by the possibility of risk and in part by the fear that the courts would not uphold the parents' right to give permission for such an investigation on their child.

Conclusions

All available evidence indicates that, in general, clinical research in children in the United Kingdom is being conducted according to ethical standards as high as those proposed by the U.S. Commission. However, the relative rigidity and brevity of the only official statements relating to research in children, together with lack of uniformity in the functions of research ethical committees, is undoubtedly hampering the acquisition of knowledge in many areas of nontherapeutic research. Uncertainty about the legality of the consent procedure seems central to the problem. A leading article in *Lancet* [14] sees no way out until a case is brought to the courts for decision; one lawyer believes that nontherapeutic procedures that are in the public interest of a child and are not in any significant way detrimental to the child's interests are perfectly legal [12]. Neither the U.K. Medical Research Council nor the Department of Health has chosen to comment. The U.S. Commission is to be congratulated for having said so much so explicitly.

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DISCUSSION

James B. Sidbury

The U.S. point of view was summarized by Dr. Ryan, who stated that the Commission had attempted to evolve a reference standard for biomedical and behavioral research as guidance for the clinical research committees in the various institutions throughout the United States. The matter of informed consent was of concern to both the U.S. and U.K. representatives. Dr. Cooke's proposal was that the family as a unit be involved in this process, sharing the burden, responsibility, and decision-making.

The U.K. representatives indicated that the standards and design of approval for clinical research resided in the clinical research committees of the individual institutions. Drs. Lawrence, Lloyd, and Weatherall emphasized their belief that each situation should be individualized. They cited the distress of parents asked to consent to participate in a clinical trial of leukemia therapy. Dr. Lloyd expressed a lack of ease with requesting and expecting informed consent on issues that are complex for the trained medical professional with years of experience. Dr. Weatherall cited examples where delay for consent would add risk to the clinical situation.

There was general consensus that good medical practice, particularly clinical research, requires open and thorough communication between the physician, the child, and the family. The concept of involving the family in decision-making was considered a good one. It was unanimously agreed that pediatricians ought to be participants on the clinical research committees when evaluations of clinical research involving infants or children is at issue.

Part 6

ROLE OF THE PUBLIC IN MONITORING RESEARCH WITH HUMAN SUBJECTS

W. E. Waters

The public has a role in monitoring research with human subjects in two distinct areas. The first concerns the selection of particular fields for research programs. These are difficult choices, but with both government money and research charities the public has helped direct research into some fields at the exclusion of others. It is difficult to justify a radical departure from present methods as most important discoveries are made "by chance," although by researchers with trained and open minds. The second role of the public concerns representatives serving on medical ethical committees. Increased representation of lay members on ethical committees is highly desirable.

Few would now confine the responsibility for research with human subjects to the investigators and subjects. In Britain the publication in 1967 of *Human Guinea Pigs* [1] was an explosive and emotional documentation of medical research. It received widespread attention in the daily and weekly press. This chapter will consider the role of the public and its representatives in two aspects of monitoring research with human subjects. The first concerns the general directions of research and the amount of research done in each particular field. The second concerns the scrutiny of individual research projects and, in particular, the nonmedical role in medical ethical committees.

Direction of Research

It is difficult to obtain detailed information on whether the direction of research is in line with what the public wants, but the two are most unlikely to be in even general agreement. How do we measure what medical research the public wants? One suggestion is to examine the contributions to the various research charities, but those who contribute in this way are a small section of society. The public, at least in Britain, is largely unaware of much of the research that is going on and has little or no knowledge of many research fields. However, the public probably would wish to direct research roughly in proportion to the incidence of disabling and fatal diseases in the community, although in practice much research is confined to restricted and apparently "academic"

fields. James Gowans, Secretary of the British Medical Research Council, admitted that the council's research priorities had little in common with the public view of priorities because most research bodies tended to fund "good ideas" that had a likely success of proving a "good" study. Gowan's view, shared I am sure by most in the scientific community, is that the neglected spheres of research are neglected because there are few good ideas for research studies in those areas. In part this is the old conflict between "pure" and "applied" research.

The organization of medical research in Britain, now mainly funded by Government, was much altered by the recommendations of Lord Rothschild in 1971 [2]. Research was divided into "basic research" and "applied R&D," and the concept of the customer-contractor relationship was established with the Department of Health and Social Security acting as "customers" and the research investigators as "contractors." The Government, acting through the political process and presumably on behalf of the public, has had an increasing role in the direction of medical research in Britain. The Department of Health and Social Security has increased its research expenditure in recent years. In 1975-76 it spent £18 million as well as commissioning a further £8 million of biomedical research from the Medical Research Council [3].

However, even this much research money from the Department of Health and Social Security and commissions from the Medical Research Council are not in proportion to the "burden of disease" in the population. Measured by a composite index based on inpatient and outpatient data, general practitioner consultations, morbidity as identified in Social Security information, and mortality statistics, expenditures on respiratory disease are less than indicated by the burden of the disease. Yet expenditures on neoplasms are more than twice and endocrine, nutritional, and metabolic disease more than six times that indicated by the burden of disease in the population [3]. Owen has given information on the changes in the percentage of the Department of Health and Social Security health and personal social services research expenditure between 1972-73 and 1976-77. Mental health increased from 9 to 14 percent, the elderly from 2 to 4 percent, and physical handicap from 1 to 8 percent. Hospital services research declined from 33 to 22 percent of research expenditure over this 5-year period.

Individual Research Projects

There have been a number of statements to guide researchers in clinical research. The Medical Research Council in 1964 issued a report on the responsibility of investigations on human subjects [4], which greatly expanded an earlier memorandum of 1953. The World Medical Assembly adopted the Declaration of Helsinki in Finland in 1964, and this was revised by the 29th World Medical Assembly in Tokyo, Japan, in 1975 [5]. These guidelines, at least in Britain, have no legal backing. The Royal College of Physicians has,

however, recommended the establishment of ethical committees, and these have gradually increased in number over the last 10 years. Again, these ethical committees have no legal standing; probably much medical research in Britain is still not submitted to the secretary of a medical ethical committee. This is not to imply that this is unethical research; many projects not submitted to an ethical committee are trivial, and submission is deemed unnecessary. The influence of these committees is, however, much on the increase. Some grant-giving bodies now require proposals for research funds to come before such committees. There is no doubt in my mind that the ethical committees have been at least partly responsible for a change in medical research that has been apparent in Britain since Papworth's exposé, which began with radio and television programs in 1960 [6] and culminated in 1967 in *Human Guinea Pigs* [1]. This change in research is now apparent to editors of medical journals in the papers they receive for publication.

The public often assumes that physicians are trained to be responsible and need no supervision in research. Yet medical ethics is at best a late entrant into most medical school curriculums, and many medical researchers regard any supervision of their research as restricting their "freedom." The concept of clinical freedom in treating individual patients sometimes seems to carry over into research investigations. Individuals involved in detailed research could lose a sense of perspective. In general, research discoveries of the greatest importance have been to a large extent "chance" events, but it is important to note that the important observations have been made by trained minds. To call the discoveries "accidents" because the results were often not envisaged is perhaps misleading. However, perspective regarding the benefit of research must be kept.

In the United Kingdom there seems to be little uniformity on the composition or methods of working of ethical committees, although the current position is difficult to review. Some ethical committees now contain lay members. I am on the joint ethical subcommittee of the Hampshire Area Health Authority and the faculty of medicine of the University of Southampton. This committee has a lay chairman (who is legally qualified) and a representative from the community health council (who happens to be a nurse). Papworth [6] suggested that it should be compulsory for ethical committees to have a lawyer, a nurse, a theologian, a laboratory or x-ray technician, and a clinician who has never played a prominent role in research. He has strong views on the failings of many ethical committees and states that "very few such committees in Britain have any non-medical representatives." At present little is published on their composition, numbers, or activities; a review of their structure and work is much needed. Newcastle analyzed 249 applications received between April 1972 and August 1976 [7] by a working group comprising a bishop (as chairman), a lay member, a nurse, a retired administrator, and another academic theologian. Eighty-six percent of the applications were given approval on the first consideration, and only one project

was completely refused ethical approval. It is important to consider the main function of these committees, which is to safeguard the interest of patients, volunteers, and the public. They should also help to protect the reputation of the investigators and the research institution or hospital, and to carry conviction and to reassure the public it is right that they have a reasonable lay representation.

Lay representation can be particularly important in helping to identify some of the difficult ethical problems of medical research, including informed consent and the manner in which it is obtained. Some disquieting facts about lack of information to patients have been reported by Gray [8].

The various research guidelines, such as the Statement by the Medical Research Council [4] and the Declaration of Helsinki [5], place stress on informed consent, but I believe it is sometimes not reasonable, or even ethical, to discuss in great detail with an ill patient all the possible implications. Whenever a doctor treats a patient he or she does not always discuss all the possibilities that might happen. Obviously there are occasions when the patient should be informed of various risks, but not with every penicillin injection or aspirin tablet. Similarly, in medical research, in a randomized clinical trial of, say, two treatments, I doubt if the complete catalog of possible adverse effects of both treatments should always be fully described. Nonmedical representatives on ethical committees can be of great help in discussing with researchers how the study should be explained to patients.

Further, they can help in deciding if all individuals in clinical trials should know that they are in such a trial at all and, if so, how they should give consent. The guidelines would suggest that they always should know, but this would mean one could never do clinical trials on unconscious patients. It would also severely restrict trials on the very ill. Do we want this? For example, there may be instances where the patient, at the height of the illness, would worry unduly about having the full details of a clinical trial explained. Imagine a clinical trial between early or later gastroscopy in cases of suspected bleeding from the stomach. Some might be of the opinion that in such examples clinical trials can never be done. However, it must be remembered that many accepted medical treatments become established with little scientific evidence, and if there is genuine doubt about treatments it may sometimes be as unethical not to do research as to do research. Claude Bernard noted, "So, among the experiments that may be tried on man, those that can only harm are forbidden; those that are innocent are permissible; and those that may do good are obligatory." [9].

However, it is not always, or even usually, easy to classify individual research projects into these three groups. The randomized clinical trial is an important tool in research, as Cochrane has so clearly shown [10]. It does have important, and often difficult, ethical problems [5], and I believe that these are best discussed with lay members on ethical committees as well as by researchers and medical practitioners with no particular involvement in research.

Ultimately we might have mainly lay committees with access to medical specialists for facts and expert assessments of risks and benefits. It is important for progress that the general public have confidence in the conduct of medical research. Lack of trust will reduce the willingness of the public to help in research, and in many projects a high response rate is desirable. In the future it might be helpful if the various research guidelines were more specific for different categories of research; for example, patients; controls (who may also be patients or healthy volunteers); studies that use or link patients' records or other personal data; and epidemiological surveys of the general population. Also the guidelines should more clearly distinguish between research procedures from which the subject was unlikely to benefit and research procedures where all patients might benefit.

In 1964 the *British Medical Journal* [9], discussing research ethics, said that "the medical profession has departed far enough from elementary principles of human behaviour . . . to show that pious general statements are of little, if any, value." Research depends on the trust of the public. Ethics must be clearly distinguished from legal considerations and from professional etiquette. Lay members of ethical committees may be particularly good at helping to make that distinction. In an increasingly questioning world, the public, through its representatives, has an important role in monitoring research with human subjects.

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ROLE OF THE PUBLIC IN MONITORING RESEARCH WITH HUMAN SUBJECTS

Michael P. Hamilton

This chapter discusses the current role of the public in medical policymaking, citing growing citizen interest in the uses of scientific and technological advances to promote economic justice, world peace, and a sound ecology. Some comparisons are made between British and American attitudes toward medical experimentation. The history of institutional review boards in America and lay representation on them is outlined, particularly in relation to emerging policies at NIH. In terms of personal experience, the chapter outlines the role of a community representative on review boards, inadequacies in consent forms, and the differing interests of the chief parties to human experimentation. Discussed finally are four unresolved problems: the limitation of financial resources for medical research funding, the immorality of transferring research to countries where ethical standards are relatively low, the selection of community representatives on institutional review boards, and the issue of compensation for injury incurred in research. The chapter concludes optimistically, noting that with a free flow of dialog between the medical community and the public, appropriate and creative compromises can be made in conflicts.

Our times are characterized by scientific and technological advances in practically every sphere of domestic, national, and international life. In the United States the times are also characterized, and this is partly in response to these new issues, by a resurgence of citizen interest and involvement in public policy decisions and in the consumerism movement. These movements focus on the proper use of new technological powers and artifacts, for what purposes and by whom, their effect on human society and the ecology of nature, and finally the funding of continuing research.

The field of medical practice and research is no exception to this activist phenomenon. It is illustrated by the public debate on such matters as the care of the dying and the Karen Quinlan case, the merits of abortion and recombinant DNA research, and the ethics of human experimentation, with particular interest in the occasional abuses. Three abuses stand out: the Tuskegee Study, where 400 syphilitic black men were kept on an arsenic and mercury treatment versus placebo long after penicillin was discovered; the use of retarded children at Willowbrook (N.Y.) Institute to test the efficacy of gamma globulin to provide immunity to a hepatitis virus and the filling of vacancies in Willowbrook with only those children whose parents were willing to consent to

their entering this hepatitis study; and the experiment by a Sloan-Kettering Cancer Research Institute investigator in which live cancer cells were injected into elderly, chronically ill patients without their knowledge.

By and large the vast majority of decisions regarding medical practice and research are still made within the medical professions; but when a new and controversial policy question arises, the implicit constitutional role of the citizenry becomes explicit. For us to discuss today whether the public should be involved in medical policy would be futile. Americans want to be involved, both on the public policy level as well as the local and sometimes individual patient level. Our task is to explore how such involvement can be most creatively and responsibly exercised. Although this phenomenon of public involvement is typically American in character, other nations, including Britain, have undergone similar evolutions and have sometimes taken leadership. However, the United States Department of Health, Education, and Welfare's guidelines for federally funded human experimentation go beyond others in their extensiveness, and the surveillance and control of research funds by Congress and governmental agencies is relatively close.

The difference between our country and the current situation in the United Kingdom was brought home to me quite vividly in a recent conversation I had with a British doctor who had just arrived in the United States. He was amazed at the lack of public trust in the competence and integrity of medical researchers in the United States, as evidenced by the HEW requirements for consent forms. He thought these regulations an example of unwarranted interference. I thought his attitude was out-of-date paternalism. Our conversation continued in a private and spirited letter-writing debate. He wrote:

> You spoke of the necessity for ethical review and informed consent, citing as justification past and horrific violations of individuals not able to protect themselves. Is it honestly thought that such deeds would be perpetrated again if the presently very restrictive attitudes were relaxed?

I replied:

> Yes, I honestly think horrific violations of medical ethics will continue to occur in spite of past experience and new guidelines. History would seem to be on my side . . . .

His hurt feelings at my lack of confidence in medical good will were matched by my surprise at his optimistic view of human nature. Our personal exchange mirrored what has occurred in the last two decades on the larger scene, where the medical profession in the United States has been subjected to more restraints than in the United Kingdom. Whether this difference reflects a greater propensity to unethical behavior among American doctors as compared with

British or whether it reflects a superior sensitivity to moral issues among Americans, resulting in controls to limit unethical behavior, is a matter I would prefer you to argue about rather than venture a personal opinion.

In this chapter I will outline the history of the review process of human experimentation in the United States, offer some personal opinions on the nature of consent forms, discuss the dynamics between the chief parties in medical research, and mention some hitherto unresolved issues.

Background

To understand how this phenomenon of citizen involvement has come to pass, we must step back a little and examine the development of policy review boards and the presence of lay representatives within them. For much of what follows of a historical nature, I am indebted to articles by Robert M. Veatch [1] on human experimentation committees and by Mark S. Frankel [2] on the development of guidelines for these committees.

Nineteenth century medical researchers could do much as they liked, following only their own consciences and whatever interpretation they might give to the Hippocratic Oath. However, the genesis of some kind of informal peer review was recommended by Thomas Percival:

> In the accomplishment of the salutary purpose (of research), the gentlemen of the faculty should be scrupulously and conscientiously governed by sound reason, just analogy, or well authenticated facts. And no such trial should be instituted without a previous consultation of the physicians or surgeons according to the nature of the case [3].

In this century the Nuremburg Code, the Declaration of Helsinki, and the World Medical Association's International Code of Ethics have developed the recommendations further by speaking of the importance of verbal patient or parent consent and the need for high medical standards in research. The conduct of medical research by investigators has, of course, always been indirectly regulated by the fact that editorial boards of medical journals exercise their own ethical standards in relation to the research findings that they choose to publish.

In 1953 when the National Institutes of Health Clinical Center opened, a guideline entitled Group Consideration of Clinical Research Procedures Deviating From Accepted Medical Practice or Involving Unusual Hazard, published in the same year by the U.S. Government Printing Office, stipulated for the first time that the written consent of the patient was to be gained in cases of hazardous experimentation. This administrative procedure required documentation of what went on in the hitherto sacrosanct privacy of the doctor-patient relationship.

In 1962 Congress passed the Drug Amendments Act, authorizing the Secretary of HEW to regulate the testing of new drugs and requiring that the consent of subjects involved in these tests be gained [4]. In December 1965 the National Advisory Health Council proposed the establishment of institutional review committees for clinical research and investigation involving human beings. Three purposes were given: the protection of the rights and welfare of the individuals involved; the appropriateness of the methods used to secure informed consent; and the risks and benefits potentially involved in the experiments. The following year, these recommendations were made requirements for grantee institutions by action of the U.S. Surgeon General.

The composition of such review committees was not fully spelled out, but an interdisciplinary group was implied. James A. Shannon, Director of the NIH from 1965-68, had already been thinking along these lines and indicated that representatives from the society at large who had ethical, moral, or legal interests should be involved with medical professionals in the establishment of guidelines for human research [5].

Parallel to these developments has been the emergence of local hospital committees with community representation addressing themselves to a variety of nonresearch type medical dilemmas, such as the selection of patients for dialysis treatment when there are insufficient machines to go around, the selection of patients for transplants, and more recently, advisory committees on the care of terminal patients.

For those interested in the constitutional and legal elements of review boards, there is a draft report available [6]. This report also treats a number of questions still unresolved about the functioning of review boards. In addition there is a report, largely a statistical analysis, on the performance of institutional review boards that was made to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [7].

The current requirements for lay representation on institutional review boards for HEW-funded grants and contracts supporting research when human subjects are involved are (quotations only relevant to lay participation follow):

> **46 106**
>
> (b) (1) . . . In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct in practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas.
>
> (4) No Board shall consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with the institution, apart from their membership on the Board.

(5) No Board shall consist entirely of members of a single professional group [8].

Finally, there have been some developments on the national scene in America wherein important committees with lay representatives have greatly influenced the recent practice of human experimentation. First was the establishment by Congress in July 1974 of a National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. With a large staff and the cooperation of many consultants, it has produced some excellent and wide-ranging recommendations. A permanent National Council for the Protection of Human Subjects is intended to replace this Commission when its mandate ends. HEW Secretary Joseph Califano set up an Ethical Advisory Board in 1977 to provide policy advice on current medical issues. Since this board plans to meet only every 3 months and has a relatively small staff to support it, their ability to provide new and creative insights is yet to be shown. Finally, Senator Edward Kennedy is reported to be trying to persuade the White House to organize a Presidential Commission for the Protection of Human Subjects to deal with medical issues that arise in the private sector, or in government research outside the jurisdiction of the Department of Health, Education, and Welfare.

The Role of a Community Representative—Personal Experiences

As previously mentioned, HEW regulations call for community representation in Government-funded human research review boards. The kind of people frequently invited include clergymen of one denomination or another, social workers involved in community health programs, or lawyers interested in consumerism and patient rights. Why one person or kind of person is invited and another not seems to be a haphazard process. I was known to some local NIH physicians as somebody interested in medical issues, so in 1972 I was invited to join the policy board overseeing the clinical trials of Trial Use of Hyper-Immune Gamma Globulin for the Treatment of Hepatitis, funded by the National Heart and Lung Institute of NIH. In 1975 I became a member, for approximately 18 months, of the medical board at the Clinical Center at NIH. This was later named the Volunteer Research Panel and is now defunct. In 1976 I joined the policy board of the Persantine-Aspirin Reinfarction Study, which was a double-blind, randomized clinical trial funded by a German drug company. Finally, in 1977 I became a member of the Clinical Research Subpanel of the National Institute of Allergy and Infectious Diseases at NIH.

I wish I had kept a record of all the interventions I had made in the discussions on the various boards of which I was a member. I must have been involved in the review of perhaps 200 protocols and probably asked for changes in the consent forms in about one-third of them. In addition I asked

questions relating to the form's design or for clarification of technical procedures and expressed doubts about the overall merit in about 5 percent of them. In about 5 percent of the protocols under review I tried to draw some general policy conclusions from what we had learned in a discussion. Around the table with me on these boards were doctors with national reputations for excellence in their field, statisticians, biologists, chemists, Ph. D.'s in esoteric fields, supervisors of nurses, and occasionally another lay representative. Frankly, it was an intimidating environment for an outsider to enter, and at first I felt like a rude, crude lion in a den of talented, sophisticated Daniels! I decided that if I were to be of any use, I would have to be honest about my feelings and questions, not be overawed by expertise, and, as far as my Irish temperament permitted, speak in a restrained and rational manner.

How well I and other lay representatives have served these boards is not for me to judge. I will say that I have been very favorably impressed and grateful for the nearly total support which was given not only to me personally, but to the recommendations I have made. I cannot recall a single instance in which I requested a change based on ethical values that, once understood, was not accepted. Sometimes the vote was close, sometimes the argumentation was painful; but mutual respect was never lost.

Most laymen's involvement in review boards focuses on the consent form since it is the chief document of the interface between the doctor and the patient. Some doctors consider consent forms cumbersome, frightening, and—because few patients understand them—of little value. I agree some are cumbersome—they deserve to be better written. I agree some are frightening—but shall we bypass the knowledgeable cooperation of the patient by not identifying the risks and discomforts involved? I agree that some patients will not understand them—but the very process of composing a good form helps the doctor be sensitive to what is happening to the patient as a human being. This last point of the effect on the doctor is one I would like to emphasize.

However, the composition of consent forms is only half the task; how well the actual explaining of that form to the patient and the gaining of his or her consent are done is equally important. Frankly, I have not yet had the time to do such followup work, and I suspect few other community representatives have or will. It seemed wise to address myself first to the task at hand of getting investigators accustomed to writing good forms. It is an area for further research.

The elements required in consent forms for Government-funded research are set forth on page 3 of *Protection of Human Subjects* [8]. I would like to see two additions: a requirement that payment or other reward for participation in the research be included, and some statement about the degree of confidentiality of data collected. Both of these elements are required in NIH intramural research.

Inadequacies in Consent Forms

As a layman I found I was more aware of certain kinds of inadequacies in consent forms than medical professionals.

Technical Language

Each profession has its own jargon. Doctors tend to forget that the patient does not necessarily understand medical terminology, even when it is in frequent use in medical groups.

Inadequate Information Regarding Pain

The following description omits reference to muscular pain:

> Liver biopsy using a hollow needle is a commonly used technique for obtaining liver tissue to analyze under the microscope. The skin over the right side of the lower chest is cleaned. The site of insertion of the needle is numbed with local anesthetic and a small cut made in the skin. You will be asked to hold your breath while the needle is quickly inserted into the liver and removed bringing a core of tissue within the needle. You will then be asked to lie on your right side for 2 hours and remain in bed for an additional 12-24 hours.

Exculpation

Some investigators, perhaps due to hospital or institutional pressure, include in the consent form a statement wherein legal liability of the institution is reduced. Apart from the fact that this is not legally possible, it places undue anxiety upon the patient. An example is:

> I hereby assume all risks, hazards, and side effects associated with or which may derive from such a procedure except where such risks or hazards are the result of negligence . . . .

Hide the Placebo

In clinical trials where, let us say, two different dosages of a new drug are being administered along with a placebo given to a control group, it is possible by use of technical language to hide from the volunteer the fact that a placebo will be used at all. Hence the patient, who may be seriously ill and desperately hoping for relief from the new drug, enters the trial with the false expectation that he is bound to receive it.

Catch-22

A phrase in the consent form is sometimes included to this effect:

> I fully understand the above information, appreciate the risks and benefits involved, and I freely consent . . . .

If the patient does not understand the content of the consent form, he or she probably does not know that fact and, therefore, should not ever be asked to say he or she does.

The Everyday Life Fallacy

> I further understand that there are no greater risks involved in these tests than my infant is exposed to in daily living.

The dangers to which infants, or others, are exposed to daily vary greatly between Harlem, Chad, Belfast, and Grosse Point, Michigan. A more precise definition of risk involved should be required.

Interpretation of Terms

In the consent form of a recent research protocol the phrase "unlikely to occur" was included. I conducted a poll of 16 doctors and other medical personnel present in the room to learn what "unlikely" meant to each of them. Their answers resulted in a range of incidence from 1 in 10 to 1 in 1 million! In the same consent form, the following terms were used with the following interpretations:

"possible"	from 1 in 10 to 1 in 500,000
"rare"	from 1 in 100 to 1 in 1 million
"very rare"	from 1 in 1,000 to 1 in 5 million
"extremely rare"	from 1 in 10,000 to 1 in 10 million

These results suggest to me that numerical incidence is a better way of communicating risk than words.

I believe the quality of consent forms is improving as investigators become experienced in composing them. My own view is that they are just as important as any other procedure described in the research protocol and that their excellence should be mandatory.

Doctor, Patient, and Lay Perspectives

From my experience in serving on review boards, I would like to offer some observations regarding the differing interests of the chief parties to human experimentation.

The Medical Researcher

The medical investigator is usually highly motivated to find a new means of treating or understanding of an illness, and to gain this information as quickly as possible. He or she wishes that the work will enhance professional status and hopes to be able to publish the research findings before any peers. In addition, the researcher is concerned for the welfare of the individual enrolled in the experiment. The ranking of importance of these motivations will vary from one doctor to another and from one experiment to another. If these are the true motivations, they explain why the doctor tries to enroll patients as quickly as possible into the experiment and tends, sometimes unconsciously, to play down the danger or discomforts visited on those patients. They also explain why researchers believe their efforts are worthwhile and why they do not appreciate being distracted by time-consuming review procedures or any regulations that seem to impede their work.

Most medical researchers are very busy people; their education is specialized and intense. Doctors spend most of their working lives talking about medicine. Their brilliance and professional prominence has been hard earned by long hours of work, but it often results in ignorance of current political realities and changes in social values.

The Patient

The patient's concern is usually to be cured as quickly as possible with as little financial cost as possible. Thus, when in a drug trial, each participant would prefer to be the recipient of the new drug being tested rather than receiving the normal treatment or placebo. In addition, one might desire to offer oneself and one's body as a source of information to help the treatment of others in years to come. As long as an unduly large reward for participation is not offered, altruism and freedom of choice can be presumed.

Patients are in a highly dependent state. They are sick and rely on the doctor as the means to health. Although one might fear experimentation, the disapproval of the physician probably is even more frightening.

John Fletcher, the clergyman mentioned earlier as working at the NIH Clinical Center, observed this phenomenon:

> It is well known that ill and hospitalized persons show a marked tendency to be dependent. Several studies show that the process of hospitalization itself greatly increases anxiety; hence if consent is requested during this period inherent restrictions on choice in the patient may be present. Patients who are being treated in an institution where research is also being done are apt to relate requests to do research to their own expectations about treatment. The patient might feel an inner reluctance to disappoint a doctor, even

one other than his attending physician, fearing that interest might be lost in "his case" [9].

The Lay Person

The role of laymen in the review of research programs is that of representatives of the community. They are likely to share in the wish to further medical research, but they are free from the doctor's status needs, free from the need to maintain friendships with medical associates, and free from the fear of speaking their mind lest it endanger employment. Finally, laymen are free from the patient's fear of sickness and the dependency on a physician.

Lay representatives, particularly ethicists, can fall into a number of traps. One reaction is that of intimidation, reluctance to voice opinions or ask questions, in a group where the person is outnumbered by professionals who speak a technical and almost foreign language. Another is to respond with arrogance, believing oneself the only valid interpreter of community opinion and moral righteousness. Education in ethics and morality does not automatically provide the "right" answers; it only imparts a sensitivity to ethical issues and some knowledge of how ethics has been practiced. Everybody on the review board shares in the moral responsibility, and everyone should contribute ethical judgments to the general discussion.

An equally dangerous trap regarding moral decisions occurs when doctors abdicate their moral responsibility if an ethicist is present. "Since our ethicist thinks it's right, then we can go ahead!" is a joking allusion to this process that I have heard. Because no person has a corner on the truth, I believe it is essential that everyone on a review board become involved in moral decisions.

Finally, the lay person or ethicist might be uninformed about national affairs and public moods and, in addition, might not grasp the purpose and design of the research nor detect the moral issues hidden within it. This type of person often turns into a nitpicker who demands that an inordinate amount of time be spent changing protocol minutiae but never recognizes the larger faults. The care and feeding of lay representatives by the medical board is essential if they are to be able to make their best contribution. Often they need assistance to identify the moral questions hidden within technical language.

Some Unresolved Problems

Limitation of Financial Resources

Doctors tend to assume that no cost should be spared to save a life and no research be left undone if it is well designed. However, it has become politically apparent that our supply of health dollars is not limitless; as a Nation we have some very difficult choices ahead. How much money should we spend on research when the standard of public health remains so low in many of our

rural and urban communities? Can we really provide dialysis treatment to everybody who wants it? When should the demands for public money for national security or natural ecology take precedence over medical research and health needs?

On these matters it is quite clear that the decisions require the involvement of more expertise than doctors alone have, or members from any other one discipline, for that matter. But doctors ought to be thinking about these matters and preparing their recommendations for public discussion. I suspect the British are further advanced than we in thinking through this matter.

Transferring Research

If a nation considers some experiment unethical in design, it is immoral to conduct that research somewhere else where those ethical standards do not obtain. To argue that such research is acceptable if the other nation's Government does not object is taking advantage of that nation's lack of standards which the investigator or funder's society has already posited as required.

It is also immoral to do research in a foreign country on a new diagnostic method for a disease if a known cure is not also made available to the patients involved. It is immoral to test a new drug that, if found effective, is not then still made available to the patient participants after the research is completed.

Difficult questions arise when useful research findings have been gained in a country with relatively "low" ethical standards. Should they be used by doctors in other countries? Should these findings be published in medical journals, thus giving the investigator prestige and perhaps encouragement to continue? The answer to these questions should be no. The long-term resolution of these dilemmas is best assured by the continual revision of ethical requirements in the light of new experimental possibilities and their enforcement through internationally agreed-on regulations on research.

Selection of Community Representatives

The choice of which lay representatives to place on review boards is not an easy one to make. To do justice to our pluralistic American culture would require hundreds of people on every board. Since that obviously is not a practical solution, how should one go about selection of membership? My observation is that practically anyone can be of help as long as he or she is not medically trained or part of some medical institution. Once so employed, one begins to adopt the values of that profession, to follow their mores, acquiesce in their pecking order, think of patients as meeting hospital and doctor's needs, and speak medicalese.

If clergy are to be invited, it would be wise to draw on the different denominations in turn. Except for the well-known differences between the churches on such matters as abortion, I do not believe it matters much which

denomination one calls on. The personal ability of the representative and his or her knowledge of current affairs is more important than his or her religious or vocational background. One needs an analytic rather than a scholarly mind, common sense more than passion.

Compensation for Injury or Death Incurred in Research

There is a growing public and professional realization that compensation should be provided to those who are injured or die as a result of involvement in human experimentation. I am referring to injury not incurred by negligence and in excess of the natural ravages of the patient's illness. In January 1977, the HEW Secretary's Task Force on the Compensation of Injured Research Subjects made strong and practical recommendations on how this might be achieved. Those recommendations have not yet been implemented. In the meantime, what do we do when, for instance, there is a known risk of Guillain-Barre syndrome occurring in killed flu vaccine research? The following exchange between a flu vaccine investigator and a lay representative on a review board poses the problem in pithy and dramatic form:

Layman:	What provisions for long-term medical care and compensation are made for volunteers who acquire permanent injury as a result of participation in your research?
Investigator:	We have no policy.
Layman:	What happens if a parent or guardian of a healthy child you wish to enroll asks you about compensation?
Investigator:	(pause) We do not enroll them in the program.
Layman:	In other words, you're taking advantage of the lack of intelligence of parents who don't ask this question? It seems that in an experiment where there is a known risk of serious injury and where the knowledge of this risk would be likely to affect the decision of the participant whether or not to participate, information regarding the lack of compensation should be part of the consent form.

As a result of this exchange, the National Institute of Allergy and Infectious Diseases Clinical Research Subpanel requested, after considerable debate, that the flu vaccine protocol involved include the following statement in its consent form.

> There is no present legal provision for compensation for permanent injury that may be incurred as a result of participation in this

study. One possible mechanism for compensation is through litigation in a court of law.

This inclusion caused a storm of protest from the California university involved for a variety of understandable reasons. At a subsequent meeting of the research subpanel a motion was made to rescind this requested inclusion. A lot hung on the disposition of this motion, and it was defeated by a vote of six to five.

The five votes represented the opinion of those who believed that the research was so important that it should proceed without the consent form information regarding compensation, which hindered recruitment and encouraged litigation. It was argued that to include this information was to make these particular research doctors suffer, while others who exposed humans to risk did not. Finally, it was wrong to begin a general policy of compensation by way of an individual research project.

I argued with the majority that the ethical issue had come to clear focus in this particular piece of research, and for the sake of volunteer participants, it had to be met. In addition, the six voters said that new general policies sometimes emerge because of problems arising in individual projects. Finally, we pointed out that we were not mandating compensation, but only providing information necessary for the informed consent of participants, as required by existing HEW guidelines.

I believe that implicit in this debate was an overriding emphasis on one side in favor of the doctors' needs and the importance of research goals. On the other side there was a primary concern for the welfare of the participants. Although a large number of people, including doctors, administrators, and lay representatives, had been involved for years in various committees to explore and promote a general policy for government compensation, I believe the presence of lay representatives among them was crucial to their deliberations. Without such representatives continuing to move the whole compensation matter through the medical bureaucracy I doubt if it ever will come to pass.

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DISCUSSION

Charles R. McCarthy

All participants agreed that advisory committees should review and evaluate proposed research. Furthermore, there was general agreement that such committees should include persons who are not professionals in the medical field. The question of whether the nonmedical participants should be called "lay members," "public members," or "community representatives" provoked considerable discussion. The most important feature of their role according to the discussants should be that they are not professionals and therefore bring a nonscientific perspective to consideration of consent forms and proposed research.

No general consensus emerged on the point, but several participants urged that the nonmedical participants should have a responsibility to alert or educate the public or the local community concerning the protection of human subjects involved in research.

It was noted that the added number of malpractice disputes and litigation in both the United Kingdom and the United States have created a climate of increased suspicion and fear. Research, like other health activities, is affected by this climate. The use of lay members on review panels tends to dampen the fear and suspicion and is, therefore, very important. Furthermore, lay members tend to make their influence felt without creating an adversarial environment that may be inimical to sound research.

Discussion turned to the question of whether it is proper for one country to impose its standards for ethical research on another. There seemed to be general agreement that an absolute relativity in ethical standards is indefensible. It could justify ignoring Nazi atrocities on the grounds that one country must not interfere with the standards of conduct set by another. Similarly, there seemed to be agreement that each country should be faithful to its own standards—even when funding research in a foreign country. Finally, international agreements should set at least minimal standards for all countries that sponsor research. Scholarly journals could do much to ensure that reasonable standards are met by refusing to publish reports of research that failed to meet international standards.

One commentator pointed out that, by improving standards in research, we may be creating new problems in the practice of medicine. For example, the University Group Diabetes Program report was critical of the use of oral drugs for the control of diabetes. Some physicians accept the evidence and have discontinued use of the drug. Some reject the evidence and continue to prescribe the drug. The majority wish to see further randomized clinical trials. But such trials are not ethical because it is unethical to ask someone to enter a

new trial in which the risks appear to outweigh the benefits. Hence we may never be able to obtain the desired information. The gap between standards for research and standards for service appears to be widening. Research is carefully regulated; the practice of medicine is an uncontrolled and unregulated process. Therefore, tightening the ethical controls over research may have a negative impact on health care delivery.

Some discussion of evaluation of review committees took place. At least three such evaluations have been published; they are referenced in Canon Hamilton's chapter.

Questions were raised about the appropriate degree of public participation in research decision-making and resource allocation. All agreed that the public should have some voice, but no one seemed to be sure how much of a voice, or through what mechanisms that voice should be audible.

Finally the point was made that a serious effort to educate all members of ethics advisory committees–particularly the lay members–concerning their duties and responsibilities should be made. Committee members cannot be expected to function well unless they are trained. At the present time little formal training is available.

Part 7
RELATIONSHIP BETWEEN GOVERNMENT AND INDUSTRY IN CLINICAL TRIALS

Louis Lasagna

In a sense it would be admirable for Government and industry to be partners in the search for new medicines, but there is inevitably an adversary relationship between these two sectors of society. Industry is the suppliant, Government the grantor (or rejector) of such boons as the right to market or to be reimbursed for drug purchases under a Federal or local health scheme.

Given these facts, how can one best contrive the rules of the game? It is generally in the interest of the regulated to have requirements spelled out, so at the least complaints can be lodged against a willful and peremptory flouting of the rules by Government. But such spelling out is not without its own dangers.

In the United States, Federal authorities have decreed as a regulatory fiat (not delineated in the relevant empowering legislation) that at least two satisfactory controlled clinical trials are required to allow approval of a new drug. In the past, this has usually meant two *U.S.* trials, regardless of the number or adequacy of foreign trials with the drug in question. Although this requirement is changing on paper to include foreign data, it is not clear to what extent the Food and Drug Administration is willing to approve new entities *solely* on the basis of foreign trials.

Why such chauvinism? It surely cannot be foreign incompetence in performing proper trials. Great Britain has led the way in such clinical experiments, and knowledge about the conduct of such trials is hardly restricted to any one land. Many countries have investigators who are performing exemplary experiments in man.

Access to Raw Data

The reason seems in large part to entail a matter of access to raw data. The FDA does not trust either industry or clinical investigators and points to past examples of fraud or error. But the United Kingdom has taken a different point of view, tending to trust physicians and drug firms. Whether this confidence is misplaced or not can be argued, but I believe that there is a real difference between the two countries in this regard.

The U.K. position is, of course, similar to that which has governed the scientific literature ever since there was such a literature. Published papers do not provide raw data sheets; and it is generally accepted by both readers and editors that authors know how to add, subtract, and divide, perform statistical tests accurately, etc. We know that in fact *this* confidence is at times misplaced, but by and large science and the public have been well served by the assumption that scientists are honest and competent unless proved otherwise.

I believe that the main bulwark against error in the past, as well as now, lies in independent replication of new facts. When a drug has been found effective and reasonably safe in different countries or in different hospitals or by different doctors in the same country, the likelihood of error becomes vanishingly small. Complicity on an international scale is much less likely than honest agreement on incontrovertible facts.

It does seem reasonable to ask for what I have called "naturalistic" experience in a country prior to registration of a drug. Genetic, geographic, nutritional, and other differences may indeed alter the responses of patients to a drug. But cannot such differences be as well (or better) explored from the application of the drug in ordinary medical practice as in another set of controlled trials?

Other Generic Problems

Regardless of the nature of a country's regulations and rules, there are generic problems that can arise from other factors. One is the quality of professional scrutiny. Even a system that uses outside advisers a great deal will have to rely heavily on the competence and attitudes of the professional bureaucrats in the agency. Obstructionism, paranoia, and downright stupidity cannot be legislated out of existence. Nor are these qualities any easier to detect and expose if the system of drug review is more or less hidden from the eyes of the interested public.

The experts consulted also pose problems. In the United States, so-called "conflict of interest" regulations have at times caused committees to be constituted that are far from scientifically or ideologically optimal to deal with the issues. Then there is the phenomenon of the busy expert who barely reads a few documents on the train or plane trip to the meeting and whose vote could be less than informed and more dependent than is desirable on the testimony of the secretariat or expert witnesses.

Ethical and legal problems will become increasingly important in the years ahead. I do not refer solely to the increasingly litigious nature of our society. I refer rather to the dilemma with which we will be faced because of our very success in coming up with new drugs. Placebo-controlled trials are not only ethically defensible, but mandatory. But can one demand such trials when effective (if imperfect) remedies are at hand? Hardly, at least as far as the

welfare of the patients in the trials is involved. However, the patients of *future* generations may, of course, gain by such trials.

What Are We To Do?

Trials comparing the new drug with a standard drug are satisfactory if dose-response relationships can be shown, or if the new drug is *superior* to the old. Failure simply to show a difference between old and new proves very little, since such an outcome can hide all sorts of problems, including the use of a population unable to discriminate between a good drug and a poor one.

I referred earlier to the possibly deleterious effects of rigid rules. One can imagine situations where the ethics of requiring even *one* placebo-controlled trial, let alone more than one, become questionable. (An example would be a new rabies vaccine or antivenom serum.) But there could also be trouble in demanding a second trial when the first has given a clean decision (such as the use of cytosine arabinoside in treating the often fatal herpes simplex encephalitis).

Another example of trouble lies in the inflexible demand that all drugs be required to meet the same standards. Surely old drugs are different from new drugs—would one insist on double-blind, controlled trials for digitalis? The "track record" of a drug deserves some credence. Surely over-the-counter drugs differ from prescription drugs in important ways. Do we really want to demand two controlled trials for every antacid tablet on the market?

What do we do about celery tablets for arthritis? Or homeopathic remedies? Can such medicines simply be controlled by limiting the claims made for them or by identifying them as ancient remedies whose scientific merit has not been proved?

Is it possible, in the case of new remedies, to speed up the approval of new drugs by step-by-step agreement on what is to be done in advance of the clinical trials? Possibly, although one wonders whether such a process might not only delay the taking of the steps but also be flawed by a change of heart on the part of the regulatory agency (or the sponsor) as the data come in.

Concerns about safety are often responsible for delays in the United States. Common side effects are easy to delineate, but the very rare or the long-delayed toxic effects are not. It therefore behooves us to make sure that our demands for hundreds or thousands of additional cases are indeed relevant to what it is we hope to detect. There are many facts about a drug that cannot be known in advance of marketing—drug abuse and the effects of massive overdose are but two. Those should be assessed by appropriate schemes for post-marketing surveillance rather than by holding drugs for ransom prior to registration by extravagant and senseless demands.

Data from industry-sponsored trials often have importance to the sponsor because of the expense involved in generating them and in their value to competitors. However, it is difficult to justify keeping important positive or

negative data from the public, or demanding needless repetition of clinical trials by different firms.

One positive solution to such a dilemma is to make freely available (as is the case already) a summary of data on the drug at the time of its approval. When a patent has expired, it would seem necessary only to insist on human bioavailability data from any new sponsor proposing to market its own version of the drug, rather than demanding new clinical trial data. This approval does not cover all contingencies, I realize, but it should meet some needs. One should not ignore the importance of moves that may seriously diminish incentives to innovation.

Industry has important responsibilities which, if properly discharged, can facilitate the introduction of new drugs. Pharmaceutical companies should choose clinical investigators and research designs of the highest possible quality. Dishonest investigators are rare, in my experience, but incompetence is everywhere and must constantly be searched for. Industry has to stand behind the data it submits, whether the information is generated in its own or outside laboratories.

Findings of data should be put together in a way that facilitates review by regulatory bodies, especially with a view toward distilling the main findings into accurate summaries. Scrutiny of those summaries could eventually substitute for the impossible task of checking every last shred of animal and clinical data.

Drug houses must also criticize and oppose with vigor irrational decisions by Government. It is tempting but unsatisfactory to let unfair or questionable regulatory actions stand, lest battle end up not only with interminable (and expensive) legal wranglings but an abiding distaste at the FDA for the company in all future dealings.

Let me take a few moments to suggest a way of thinking about controlled trials that deserves consideration by Government, industry, and the medical profession. The basic components of my argument are simple:

1. The controlled trial is a mechanism for rejecting the null hypothesis, not for generating conclusions that are necessarily extrapolated to ordinary medical practice. This is so not only because the optimization of circumstances for establishing efficacy may lead to choice of a highly "atypical" experimental population, but also because consent procedures, the reality of availability of patients, and the logistics for their study, etc., all can lead to enormous "volunteer error." Surely no one can pretend that he has ever studied a random sample of the universe of patients suffering from any disease or symptom.
2. This does not mean that the results of a controlled trial are *irrelevant* to the real-life practice of medicine, but it does mean that the results might need modification as one attempts to

apply them to patients who are substantially different from those in the trial. For patients with milder disease, for example, the drug in question may not be needed, not worth the risks, or needed in smaller doses. For patients with more severe disease, the drug may have to be given in higher doses, or may be ineffective at any dose.

3. The obvious conclusion—if you accept the two previous points—is that we must develop new strategies for moving from the "hothouse orchid" environment of most randomized controlled trials to the "field daisy" environment of the practice of medicine.

We have developed the formal controlled trial to a high level of art and science. It has served society well, but it *cannot* do so to answer questions it is not suited to answer. We must move on to the next level of drug evaluation, and to do so may require the talents of individuals who have not in the past played much of a role in deciding whether a drug should be marketed or not.

Finally, a word about guidelines. A number of groups have tried to come up with rules for playing the clinical trial game in different therapeutic areas. To the extent that an area has well-developed, generally agreed-upon methodology, such a spelling out should do some good and cause little harm. Such is not the case when methodology is far from worked out or agreed upon. In any case, rational deviations from official protocols should be encouraged, lest progress in improving clinical trials be stopped.

RELATIONSHIP BETWEEN GOVERNMENT AND INDUSTRY IN CLINICAL TRIALS: NEED AND PURPOSE FOR RULES AND REGULATIONS

Desmond R. Laurence

Regulation of drugs by statute has inherent characteristics that cause the regulatory body to increase its requirements, even where scientific justification is weak, and with little or no regard to cost. The trend to impose safety requirements that are excessive or unbalanced in relation to their cost and to the benefit they confer will continue until health politicians are given an opportunity to sponsor rational regulation without risking damage to their public reputations.

There is increasing opinion that the requirements of current drug regulatory authorities may be excessive and only partly based on science, and that now is the time for radical review and reform. There is a need for:

1. Evaluation of benefit/risk/cost by independent scientists internationally.
2. Availability to those who suffer adverse effects of new drugs, not only in premarketing research but also during any period of postmarketing surveillance, of a speedy, efficient, and generous "no fault" or "strict" liability system to compensate for drug-induced injuries.
3. Continuing explanation to the public and to politicians of a balanced picture of benefit/risk/cost of drug research and development.

To state the purpose of government rules and regulations controlling development and introduction of new drugs is simple: to protect the public against risk, exploitation, and incompetence. In such an area, where action must inevitably infringe the liberty of several parties (developers, doctors, and patients), Government has waited for the need for intervention to become imperative before it has acted. Although the United States learned its lesson in 1938 with the Massengill/sulfanilamide accident, most of the world introduced comprehensive controls only after the thalidomide disaster of 1960-61.

In the United Kingdom we are still using what is essentially the same procedure as that developed in haste and inexperience after thalidomide, although it has since changed from a voluntary to a statutory system and has added concern for efficacy to that for safety. Eighteen years after that disaster is an appropriate time to look at our regulation, its characteristics and extent, and to ask ourselves whether we have developed an efficient benefit/risk/cost system.

As an independent adviser, I joined the old voluntary organization for drug

regulation, the Committee on Safety of Drugs (Dunlop Committee), in the year of its establishment (1964). I served until it was translated into the statutory Committee on Safety of Medicines in 1971 and saw the changes in attitudes and practice that accompanied the imposition of law. Over the years I have been involved in the debates on what regulatory action should be taken on all the problems that, sometimes with dramatic suddenness, are put before a regulatory body. I have now left the interest, excitements, tediums, and frustrations of the Committee on Safety of Medicines for the supposedly higher levels of regulatory policy, the Medicines Commission. One of its first tasks under the Medicines Act of 1968 was to advise the Secretary of State for Health that a Committee on Safety of Medicines should be appointed to succeed the previous voluntary arrangement. I am here going to argue that our present system of drug regulation is not as efficient as it should be, and I am going to offer for discussion some reasons why this may be so and some proposals as to what might be done to improve it.

I shall take it as common ground that some form of government regulation of drug introduction is both desirable and necessary. My theme will be as follows:

1. That regulation by statute has inherent characteristics that cause the regulatory body to increase its requirements, even where scientific justification is weak, and with little or no regard to cost.
2. That the trend to impose safety requirements that are excessive or unbalanced in relation to their cost and to the benefit they confer will continue until health politicians are given an opportunity to sponsor rational regulation without risking damage to their public reputations.
3. That current drug regulation is excessive and only partly based on science and that it now requires radical review and reform. To achieve this we need:
   a. Evaluation of benefit/risk/cost by independent scientists who are not merely experts but authorities (I use the distinction of Melnick et al. [1]).
   b. Availability to those who suffer adverse effects of new drugs, not only in the premarketing research but also during any period of postmarketing surveillance, of a speedy, efficient, and generous "no fault" or "strict" liability system to compensate for drug-induced injuries.
   c. Continuing explanation to the public and to politicians of a balanced picture of benefit/risk/cost of drug research and development.

Problems of Statutory Regulation

In 1964 the newly set up Committee on Safety of Drugs told industry that in effect the committee intended to operate in a liberal and understanding fashion, that it was a body of reasonable people whose only desire was to protect the public, and that it would only be necessary for drug developers to put forward reasonable proposals. Although the intention was applauded, this statement was, of course, no use to industry as a way of conducting their practical affairs. Much of drug testing, especially safety testing, is a matter of opinion. Industry could not afford to risk being told, after completion of years of work, that the committee felt, for example, that the chronic toxicity tests should have been done differently or more extensively and that the applicant should start again. Requests that a plan of research for individual projects be approved in advance were, naturally, declined as impractical by the committee. The result was the committee's first set of guidelines, which were careful to indicate then, as now, "In the interpretation of the following guidelines it must be appreciated that they are not rigid requirements and may not be universally applicable. Interpretation should therefore be flexible and related to the proposed use of the drug."

Guidelines inevitably become close to minimum requirements. A developer who does not follow them does so at peril to his research program. In the face of an adverse decision, appeals to stated intentions of flexibility may indeed succeed, but they may fall on deaf ears. Advisory committees have their moods; sometimes matters of opinion and of judgment are decided differently on different days. Everyone knows that this must be so, although it is not widely spoken about; it is, no doubt, one of the reasons why we have a good system of warning applicants of impending adverse recommendations and of appeals. It is a bold or rash research director who does not tell himself that prudence counsels the performance of tests mandated by the guidelines, even where he or she doubts their value. The expense of a regulatory setback can be greater than the expense of extra tests.

As time has passed industry has asked more questions on toxicity testing, species of animals to be used, doses, duration of tests, oncogenicity, mutagenicity, clinical trials; the list is extensive. The committee has responded as it should, with detailed decisions where appropriate. For the broader areas it has set up working parties jointly with industrial scientists to prepare guidelines.

The meetings of such working parties are not divided into industrial workers seeking to minimize requirements and academic and other scientists seeking to maximize them. It is my experience that for specialist scientists the interest of the application of their expertise to the fascinating process of prediction from animals to man arouses enthusiasm that overcomes any loyalties to employers incompatible with their science. I have been interested to see industrial scientists willingly imposing on themselves the burdens of dubiously predictive tests, particularly in areas of reproduction and oncogenicity. The result of all this is a relentless ascending spiral of requirements as knowledge of what *can* be

done and of what *may* happen advances. Testing for reproductive function provides an example. In 1964 we expected dosing of pregnant animals only during the period of organogenesis; now we expect to start dosing both sexes before mating, to continue throughout pregnancy, to wean the litter, to rear some, and to breed from them. In addition, events occur and problems arise that conspire to increase testing requirements; for example, problems of oncogenicity and the oculomucocutaneous syndrome of at least one beta-adrenoceptor blocking drug, problems with renal toxicity of nonsteroidal anti-inflammatory drugs, etc.

Another issue of increasing importance in preclinical testing is the ethical aspect of employing large numbers of animals in tests of doubtful relevance to man. There is growing opinion among those who are not opposed to all tests in animals that their use should be confined to areas demonstrated to have relevance to man. At present in the United Kingdom there is a demand for Government to sponsor an inquiry into the need for and amount of research conducted in animals. We should not ignore this concern.

In the special area of clinical trials I shall discuss three examples of aspects where disagreements have arisen between regulatory bodies and those within and without industry who develop and test drugs.

First: The extensive requirements in the United Kingdom for pharmaceutical, chemical, and analytical data before clinical trial, which industry has long criticized as unnecessary. Industry notes that these areas are under development and that extensive detail is not available and is even considered unnecessary by other countries. Clinical trials of drugs developed in the United Kingdom have often been well under way in other countries, while the U.K. authority "is still querying details which are, at best, on the borderline of relevance" [2]. Debate in this area persists. There is a genuine difference in what the two sides consider to be necessary for safety.

Second: Recently concern arose in the regulatory body because some developers were submitting applications for marketing drugs (product licenses) for indefinite use in man, e.g., antihypertensives, on fewer and fewer patients treated for shorter and shorter periods. A discussion followed as to reasonable size and duration for clinical trials of such drugs. The consensus was that, to prepare a good medical data sheet on efficacy, dosage schedules, and the more common adverse reactions, it would be desirable to have treated about 100 patients for about 1 year. The regulatory body's sole objective was to help drug developers plan their studies and avoid premature applications with their consequent waste of time and effort. But when this view was intimated to industry, there was an outburst of indignation about excessive and arbitrary regulation being imposed without consultation.

This incident occurred at about the same time as a proposal from a working party on oncogenicity testing that no drug should be given to human beings for longer than 6 months unless it had undergone standard oncogenicity tests. In

other words, if clinical trials are not to be interrupted at 6 months and re-started later, some oncogenicity studies will have to begin before it has been decided to give the drug to man.

It is easy for a regulatory body to find itself in situations of this kind resulting from advice of different expert groups. Although I have no doubt this particular problem will be solved by discussion, it underlines the increasingly recognized need to take a hard look at the scientific basis of drug regulation in relation to the practicalities of the process of drug development and its social importance.

Third: The proposed FDA regulations on clinical investigations address the obligations of sponsors and monitors [3]. In 1976 the FDA was allocated $16.3 million and authorized to appoint 600 new staff members (the European mind reels at these figures) to expand monitoring of preclinical and clinical research related to FDA-regulated products.

My reason for discussing FDA activity here is that its proposals will apply to other countries if data generated outside the United States are to be accepted by the FDA. The drug industry is international, and it is vital that data be accepted internationally wherever scientifically appropriate. (The new group of histamine H_2-receptor blocking drugs was discovered and developed in the United Kingdom, but researched in the laboratories of an American drug house.) Some proposed regulations may have to be modified where conditions in other countries are so different that some aspects of the FDA regulations cannot be applied.

The general intentions of the FDA are above reproach. Of course, bad clinical studies are done, there have been cases of falsification of data (in both our countries), and we do ignore pompous people who are insulted if they and their work are scrutinized. The FDA preceded their regulations with a survey of clinical investigations (concluded in 1974) that found, as expected, that "grossly violative practices are infrequent, minor deficiencies were frequent." Yet we hear in 1978 that there is enough concern for the FDA to mount a further investigation.

Monitoring of clinical studies is proposed in quite extraordinary detail. I cannot help wondering who the monitors will be, for if they are incompetent we are better without them, and if they are competent they have skills that could be better employed.

In the early days of motoring some governments decided that in the interest of public safety close monitoring was required. Each car was preceded by a man with a red flag. No doubt this prevented speeding, but it was soon abandoned. We all know the terrible current loss of life on the roads, and we all drive with more care for the regulations (and perhaps even with more skill) when we know we are being monitored by a policeman. Why does no one advocate that each car on the road be monitored by a police car? We all know why. There is a lesson here for drug regulation.

We limit the policing of society because it is expensive and because the public can see for itself what it involves and tell the politicians what they want in relation to benefit/risk/cost. But drug development is not so easily comprehended by the public, and the checks to overpolicing do not act.

I have referred in passing to the moods that can affect committees and to the enthusiasms that affect experts whose advice is sought. Plainly, the tendencies of drug regulation cannot be spoken of as if they were independent of the individuals who conduct the business. After forming these views I shall express here, I was interested to read an article by Lord Ashby [4] that explained the background to what I had been experiencing; in taking decisions we are influenced by the desire not only to avoid risk but also to avoid regret later: "risk avoidance" plus "regret avoidance."

There are certain important characteristics to governmental regulation of drugs in the United Kingdom. The minister responsible:

1. Can be questioned publicly in Parliament.
2. Is obliged to depend for his reply on civil servant and expert advisers.
3. Receives no credit when a good drug goes into general use, but can receive severe criticism when an accident occurs.
4. Does not find any important political principle or party advantage in good drug regulation.

It would be a matter for surprise if in these circumstances not only the politicians but also the civil servants and expert advisers find themselves seeking to minimize risk, although it might not seem so to them as they work. This innate tendency toward immediate risk avoidance can be further enhanced by the desire to make recommendations that will also not be a subject of later regret, "regret avoidance." The pressures of risk avoidance plus regret avoidance are real and can lead to suffocating overregulation. As Ashby [4] remarks, "neither politicians nor the civil servants advising them like making enemies; their temptation to indulge in regret avoidance is strong, . . . the decision-maker himself is liable to have an instinctive bias to risk aversion and dilution of responsibility."

The kind of continuing pressure on drug regulators was illustrated within a few months of marketing of the first histamine H_2-receptor blocking drug, cimetidine (Tagamet) by a Member of Parliament's publicly asking the Secretary of State for Health about adverse reactions to the drug. There was no public anxiety about this drug, and a parliamentary question of this kind is unusual. The politician could easily have gotten the information privately from the developer or from the Committee on Safety of Medicines; but for reasons I cannot fathom, he chose to get it publicly in Parliament. Inevitably those in drug regulation as well as drug development are affected by the knowledge that they are being watched closely by people ready to criticize at any opportunity

but whose motives are not always obvious. "Miracle" drugs are a media wonder for a day or two; their hazards provide material for months, with scope for moral indignation added. But workers in drug regulation, independent advisers as well as civil servants, can never forget how they came to be where they are. Their prime function has been protection of the public through smooth operation of the law and such detailed policies as are formulated by the regulatory organization to carry out the intention of the law.

I myself have a clear recollection of saying with emotion at a meeting of the Committee on Safety of Medicines, "Let us remember that it is thalidomide that brought us round this table, and let us remember our title, the Committee on *Safety* of Medicines."

It is also true that the atmosphere in a decision taking committee with detailed data on particular chemicals before it is very different from the atmosphere in a general discussion on the philosophy of benefit/risk carried out where there is no immediately pressing question of making a decision affecting the safety of individuals. The risk of public outcry if a wrong decision is made adds to this dilemma.

Continuously sitting in judgment on the laborious work of others carries an occupational risk of developing unrealistic standards. It is too pleasant to be able to demonstrate to colleagues that one has a razor sharp mind that never misses deficiencies and always thinks of better experiments; that one has high standards that cannot be compromised; or that anyone who advocates less has low standards, is the victim of sloppy thinking, and might even be callous to human suffering. Certainly pressures form our attitudes, and those undertaking the responsibilities of drug regulation are subject to these pressures and are influenced by them whether they are conscious of this or not. Despite these pressures, regulatory bodies should seek to smooth the path of valuable new drugs and even to explain to the public that benefits exact a price in risk since they represent relatively new ideas.

Rational Regulation

It is often claimed that politicians will seek absolute safety in drug testing and will demand that all thinkable precautions be taken, regardless of whether there is in fact good evidence that those steps contribute to safety. Certainly the natural tendency of people who are publicly accountable is to act to avoid any possible criticism in the future (risk avoidance and regret avoidance). But politicians do know that absolute safety is unattainable, even if they seem to behave otherwise.

In 1963 in Parliament, discussing the setting up of the Committee on Safety of Drugs, the Minister of Health stated "emphatically that when they used the word 'safety' . . . they should not be understood to mean 'absolute safety.' Safety in this sphere was relative whatever might be the arrangements, whatever might be the law. It was relative to the illness, and . . . there was no system

that could be devised which would make doctors or scientists aware of what medicine and science had not yet suspected" [5].

Politicians naturally rush to fulfill the expectations of the public on whom their careers depend; and they respond to what they interpret as pressure from the public in general, although that pressure is largely the result of efforts by special interest groups and the mass media. If we want politicians to act sensibly in areas where there is public anxiety and outcry, they must be protected from unreasonable criticism. Their path must be made easy, or they will not act sensibly.

I suggest that it will be politically impossible to do other than to maintain or increase regulatory requirements along current lines until health politicians are convinced that there is public understanding and acceptance of the need for review and change. The public must accept the fact that risk is inevitable and that it is in the interest of the sick that certain risks be taken. This means that the mass media, representing the public, must accept and propagate the attitude that risk is inseparable from drug development and use and that the risks of drugs are as socially acceptable as risks of surgery, and a great deal more acceptable than the risks of smoking and alcohol. This is a task for scientists with a flair for communication. But they cannot succeed unless one special condition is met.

The public attitude toward industrial drug developers must be changed and be separated from that of the multinational corporations, which have a bad public image. I am concerned here only with drugs.

It is relevant that in the United Kingdom elected Members of Parliament were active leaders in associations of patients that negotiated, in a blaze of publicity, compensation for victims of thalidomide. More recently (1976) in the case of practolol, where the initial offer of the company preceded any outcry, this did not prevent a similar process during which the compensation was considerably raised. It seems unlikely that it can ever be acceptable to leave it to the pharmaceutical firms to set up or handle processes of compensation. The apparent need for associations of damaged patients has had a big effect on public attitudes. Such associations must be made manifestly unnecessary, and that will only be achieved if the public can see that the pharmaceutical industry accepts liability for any casualties of its development activities and that the decision to compensate and the amount of compensation are delegated to independent assessors. Indeed, schemes for "strict" or "no fault" liability for manufactured products, including drugs, are being introduced in many countries and are expected in the United Kingdom. The pharmaceutical industry has generally accepted that this is a responsibility it must meet.

Review and Reform of Drug Regulation

To achieve radical review and reform of drug regulation in light of current science and the experience of the past 18 years we need:

1. Evaluation of benefit/risk/cost by independent scientists on an international basis (for drug research and regulation is now an international activity) considering what is necessary and, equally, what is not necessary.
2. Availability to those who suffer adverse effects of new drugs, not only in premarketing research but also during any post-marketing surveillance, of a speedy, efficient, generous "no fault" or "strict" liability system of compensation for drug-induced injuries.
3. Continuing explanation by scientists to the public and to politicians of a balanced picture of benefit/risk/cost of drug research and development.

If these three conditions are met, we can have some hope that it will become politically possible to base drug regulation on scientific considerations alone. It is in the public interest that this be achieved.

There is evidence from many sources of growing concern among scientists that drug regulation may be suffocating new drug development and that it is desirable that independent scientists play a greater part in formulation of national policies. This evidence stems from various sources including Dr. Lasagna's Center for the Study of Drug Development [6], industrial scientists [7], university biological and political departments [1], and European academic and industrial scientists [8].

It is known that official regulatory organizations are engaged in regular consultation internationally in Europe (European Economic Community, Council for Mutual Economic Assistance, World Health Organization European Region [9] all have annual meetings), and across the Atlantic. At these meetings the tendencies that I have discussed are operative. The official drug regulators have access to funds for regular meetings.

International scientists independent of government service certainly meet each other from time to time and they recognize the problems, but there are no regular meetings that allow systematic reviews and the development of new, rational policies.

Jack [7] categorizes risk in formal clinical studies as relatively low in the early restricted and carefully monitored stage, intermediate in the late formal clinical trials, and high after marketing, when the drug is used in a larger, heterogeneous population with less supervision. This is a generally accepted view. He points out that British regulatory procedures are not consonant with this: they are more detailed where the risk is low and less detailed where it is high.

Nobody objects to strict regulatory requirements if they are effective. For instance, the need for postmarketing surveillance is now generally accepted, but it looks as though regulatory bodies are going to add it to the edifice of existing requirements without review of whether its institution could be

accompanied by some relaxation in the lower risk areas. We cannot afford to continue expensive practices that are not efficient. A colleague remarked to me recently that if all drug development were done in government laboratories and paid for with tax monies, there would be urgent discussions on whether value for money was being received from escalating budgets. But the testing takes place in private industry, and global figures are not available or are not in the right form, so no such concern on cost/benefit is shown. There is a general feeling that drug prices are too high, so it is the public who pays the bill in the end in both cases.

Melmon [10] made two remarks in his article that are particularly relevant to my purpose. He writes that he considers that academicians can and must help to create sound legislation and assume authority in scientific matters. He adds that his disappointment is not with Government but with scientists and their inaction. He is right; Government is a sailing ship that has been following the strong wind caused by public reaction to thalidomide. It is only likely to change course if a new wind of science blows from a different direction.

Melnick et al. [1] make a useful distinction between an "expert" and an "authority." An expert is recognized by his peers; an authority is one whose expertise is recognized outside the scientific community, one who is called on to give advice and counsel to the public. It could be said that many experts are now vocal, but they still have not seen their way to influence Government directly and via public opinion, as Melmon advocates. This will be achieved when more experts become authorities (as defined above), for unless they do we shall see bad policies continuing to the accompaniment of experts wringing their hands. People who actually labor and take the responsibility for developing and testing drugs and choosing and using them to treat disease are the people who should set the standards for drug regulation. If there are grounds to fear that there is overregulation, these are the people who must go out and influence the public and Government. When public expectations are in accordance with reality we shall have good drug regulation, not before.

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DISCUSSION

Robert J. Temple

The discussion following Dr. Lasagna's and Dr. Laurence's talks focused on the evidence required before a new drug may be marketed and, specifically, on the case of sodium valproate as an illustration of some of the differences between the United States and the United Kingdom and of the judgmental elements that are always part of such decisions.

Dr. Booth took issue with Dr. Laurence's discouraged view of the British legislation, urging that this relatively recent legislation be given a chance to "go" for a while before major changes are attempted. He felt the new legislation, while not perfect, was a vast improvement and had led to strong and effective international relationships with the United States and Canada through the tripartite agreement.

Dr. Laurence denied suggesting that legislation needed to be altered. The legislation, he noted, simply says that the efficacy, safety, and quality of drugs shall be controlled; it does not say how that should be done. He felt the requirements under the legislation, however, were escalating and were going too far. The cost of developing novel chemicals is about $55 million, and probably only 22 firms in the world can contemplate that "with reasonable equanimity." Under the existing legislation there is a tendency to "add, add, add," which is probably not scientifically based. It is this pattern he would like to see altered, not the legislation itself.

This point was echoed by others. In response to a question by Dr. Chalmers, Dr. Lasagna agreed that, as "someone who. . .played a small role in helping to get the '62 amendments passed," he was appalled at any movement to repeal the effectiveness provisions of the Food, Drug, and Cosmetic Act and considered such a move as unneeded, as were efforts to give new powers to the FDA. Rather, he believed the act was generally a good one, although not perfect. He said he found most of his arguments with the agency had to do with implementation and regulation. He knew of no reputable academic clinical pharmacologist or drug industry leaders who had advocated repeal of the law.

The discussion then turned to Dr. Ryan's question regarding possible expedited approvals and the recent public clamor for sodium valproate, which had been unavailable in the United States despite a general view that it was effective. Dr. Lasagna found himself both encouraged and discouraged by the valproate, Laetrile, and saccharin episodes, each of which showed that the public can become aroused and impassioned and begin to say to regulators, industry, academia, the medical profession, and Congress, "A pox on all your houses. We don't trust any of you. Tell us the facts, but don't tell us what to

do." Although he found that situation encouraging in a democracy, democracies do make errors. Thus, while he thought Congress made the correct decision on saccharin, he could not be encouraged by the Laetrile episode. While he felt valproate had been well worked up and deserved "expediting," he warned that if a deserving drug can be expedited, so can an undeserving one. While he realized FDA would say it would not approve such a drug, FDA is subjected to constant political pressures, especially from Congress, and he therefore remained concerned.

Dr. Temple explained that valproate had been denied approval initially because the statutory requirement for well-controlled studies showing effectiveness had not been met. Shortly after that decision, other studies were completed, and the drug was approved. Dr. Ryan's question was whether approval could have been granted earlier, when "everyone knew" valproate worked but controlled studies were not complete. Under present law the answer is no. Legislation now before Congress, however, would, under very specific and limited circumstances, permit different kinds of evidence (i.e., evidence other than well-controlled studies) to be a basis for provisional approval of a drug for marketing. This would apply only to drugs that are lifesaving or intended for an extremely serious illness, and the drug would have to have a tremendous advantage over other kinds of therapy. Under such conditions, the drug could be approved, and well-controlled studies performed afterward. This feature of the law may help resolve the problem of the drug that is known to work but cannot yet meet the statutory standard; it clearly raises, however, the concerns Dr. Lasagna described.

Dr. Laurence pointed out that Britain had marketed valproate on the basis of studies available, which were considered adequate. He found the difference in judgment interesting. Britain felt there were reasons to think it was effective in patients not controlled on other agents. Studies were confined to this population, and general studies in epilepsy were not required. Yet, the same studies were found inadequate by the United States. He wondered whether this was an example of having a general rule of what constitutes an adequate study and then applying it across the board to absolutely everything.

Dr. Lasagna added that it appeared new chemical entities for which applications are filed almost invariably get approved eventually. He thought the delays are due to arguments about what constitutes enough evidence of efficacy and safety, which is where men of good will can disagree. He also felt this judgment was flexible in some cases, suggesting that valproate was pushed along faster than Dr. Temple's discussion implied because of the "impressive media work" backing it.

Dr. Crout of the FDA then sought to clarify the sodium valproate situation, which he viewed as a classical example of the difference between decision-making on the basis of expert opinion and the FDA's evidentiary standard of the adequate and well-controlled trial. He agreed that there was a great deal of political and media pressure and this had had two effects: first, it persuaded

Abbott Laboratories to move its own research program along and get a new drug application together; second, it caused the FDA to expedite its review. What the FDA sought to avoid, and did avoid, was changing the evidentiary standard, because the FDA "feared the specter of any number of drug firms seeing that the combination of publicity, an outside pressure group, and congressmen writing can erode standards for drug approval." The FDA and Abbott thus tried to move fast, but the FDA also tried to be "as picky with valproate as we are with all drugs."

After the FDA received the valproate application, it was taken very promptly before that agency's advisory committee, which unanimously recommended approval of the marketing application because the committee members thought the drug worked. Everyone in the FDA agreed that valproate was an anticonvulsant and that it worked. But when the studies submitted were compared with the standards of a well-controlled study, the studies did not meet criteria that had been set up by the same advisory committee. For example, the committee had previously said (in its anticonvulsant guidelines) that anticonvulsant drugs should be approved for specific types of epilepsy, because different anticonvulsants had different effectiveness in the various types. Petit mal seemed the type for which valproate was likely to be best. But when the FDA looked at the few controlled trials of the drug (valproate had been worked up in France in the late 1960's and early 1970's, and most studies were uncontrolled), there often were very few cases (six to eight) of petit mal. These trials usually compared valproate with a positive control, ethosuccimide; and six to eight patients is very small for a positive control trial. Often, concomitant medication was present, which can also be a problem. For example, valproate leads to increased blood levels of phenobarbital; it appeared possible this increase, rather than the valproate, might explain improvement seen. By the time various cases and trials were dropped for various reasons, "the trials fell apart." It was not that the trials were wrong; they could not meet modern evidentiary standards. The FDA thus had an advisory committee recommendation for approval, but a recommendation that did not identify any adequate and well-controlled trials. The committee had provided "a conclusion without the supporting evidence," the worst kind of advice you can get from a committee when faced with a "hot" problem. The FDA asked for another trial, which fortunately was under way—a telemetry-monitored trial, and a good one. The data came in January 1978, and the drug was approved in February. Dr. Crout explained that he had provided the details of valproate so the group could get "a feeling for some of the agonizing over trials and some of our attempts to be very precise on the evidentiary standard because valproate signifies. . .the crux of the difference between the United States and the United Kingdom in its decision-making."

Dr. Laurence suggested that the FDA was "a prisoner of [its] good intentions. . .you explained it absolutely perfectly. . .it was a good drug and with lots of evidence but [the evidence] was not of exactly the right kind. . .so you

say 'we can't act.' " Dr. Crout explained that it was a greater failure than "not exactly the right kind." When the cases of petit mal were collected there were so few that in a positive-control study (evaluating sameness, not difference) the statistics do not permit a conclusion that a lack of difference was demonstrated. Dr. Crout emphasized that the FDA had not "invented some fake standard." Valproate did not meet the prevailing standard. Once the proper data were available, valproate was approved, and in less than the 180 days allotted.

Dr. Laurence explained that the United Kingdom also had seen "the problem of the French evidence" and had asked for a small, careful trial in patients inadequately controlled by current therapy. The trial came out positive very quickly.

Dr. Crout explained that FDA had seen a similar trial. Patients resistant to ethosuccimide were randomized to valproate or ethosuccimide. If they did not respond to the initial drug they were crossed over. Unfortunately most of the patients given ethosuccimide responded to it, even though they supposedly were resistant. Thus the entrance criterion had not worked properly.

Dr. Lasagna found this incident "surrealistic." He felt that if an advisory committee, to a man, says a drug is effective and the official criteria are not met, you have either bad advisers or bad criteria.

Dr. Crout disagreed. He quoted Otto Warburg as saying, "I spend 10 percent of my time convincing myself of what the truth is and 90 percent convincing everybody else." The U.S. regulatory standard of adequate and well-controlled studies requires trials to be documentary. The requirement may go beyond the required amount of documentary evidence that is usually necessary to convince an expert that something is working. Our advisers generally bring to their decisions their experience and intuition and would routinely approve a drug in their area before the evidence is all in, although they might want to limit it to certain experts.

Dr. Lasagna responded that if the advisers are generally wrong the requirements for additional evidence are well taken; if, on the other hand, they are almost invariably right, one wonders whether the requirements for evidence are not excessive.

Part 8

INTERNATIONAL STANDARDS IN CLINICAL RESEARCH

C.C. Booth

Internationalism is more than an encounter between European and North American peoples; it reflects the meeting of peoples of different cultures that leads to greater understanding. Science provides the international forum where all peoples can meet on equal and common ground. In the field of medical research, internationalism is fraught with both political and scientific difficulties, and we in the West often end up branded as scientific or medical imperialists.

Internationalism in medical research is promoted by the same forces that disseminated the early findings of medical science (although some have broader implications because of modern technology): clinical research, common language, medical societies and journals, and control of health services and medications. We in the West, however, must not overlook the fact that what is good in one environment might not suit the environment of the developing world. It is important not to lessen the spirit of internationalism by overlooking the needs and desires of developing countries.

Internationalism has been the utopian dream of idealists ever since the confines of the existing world became more generally known in the 18th century. In December 1780, Benjamin Franklin received a letter in Paris from his one-time London physician calling for the "institution of a college of justice where the claims of sovereigns should be weighed, an award given, and war only made on him who refused submission. . ." [1]. The past 200 years have not yet realized this dream, and current events in the eastern Mediterranean region and elsewhere should remind us that nationalism rather than internationalism will guide the destinies of the peoples of the world for many years to come. In the devolutionary world in which we live in Europe, where Basques, Scots, Bretons, and Welsh all seek their own narrow nationalism, we could be thought to be departing from the united Europe envisaged by Maurice Schuman. Yet although this is true to a certain degree on the political scene, it can also be emphatically stated that in medical research there has been during the past 10

I am particularly grateful to Dr. E.L. Harris of the Department of Health and Social Security for his assistance in guiding me through the Medicines Act of 1968 and the work of the Medicines Division.

years an important "rapprochement" in the countries of Europe, and not just in the European Economic Community. This has also been true all over a world where air travel has made neighbors of once distant and alien peoples.

When we talk of international standards in clinical research we must first define our terms. What is *international?* What do we mean by an *international standard*, and what is *clinical research?*

Internationalism

To me, internationalism means a meeting of peoples of different culture, not merely an encounter between European and North American people who share the same cultural background and who, therefore, have a solid base for mutual understanding. The North American experience was created out of that policy so well enunciated by Tom Paine when he pleaded that America should give up dependence on a small island 3,000 miles away, cut itself off from that "Royal Brute of Great Britain," and claim brotherhood with every European Christian. Like so many of his countrymen at the time of the Revolution, he ignored the Jewish contribution to the cultural identity of Europe and North America; he might well never have known of Chaim Solomon. But the policy that he advocated created the greatest of the world's modern republics.

What now is important in the international scene is that Europeans and North Americans meet and understand Indians, Africans, Chinese, and Arabs, for example. For among these people, with ideas of life and the world so different from ours, there are differences in wealth and culture that are significant in dividing the globe into those areas so facilely classified as "developing" or "developed." Surely, it will be said, science (particularly medical science) provides an international forum where all peoples can meet on equal and common ground. To a Westerner, this seems axiomatic, but the science of Western man represents something that has long been part of his cultural heritage, derived from Greco-Roman origins, from the Arabs who maintained the light of knowledge in their places of learning during the Dark Ages in Europe, and more recently from the Renaissance and the Industrial Revolution. Others, however, who do not share this cultural heritage reject the Western materialistic concept of life and often reject with it the achievements of medical science, not because they do not understand it but because they see it as a dangerous imposition of part of an alien culture. Such attitudes are not uncommon in some parts of the developing world today, where international understanding is vital in achieving the common goals of eradicating or controlling poverty and disease.

International Standards

International standards, like any other standards, can be considered in terms of either quantity or quality. Quantity standards do not present any great problem in international terms. In the medical field organizations such as the

World Health Organization have been particularly effective. Hemoglobin standards, for example, are now internationally agreed, and in the particularly important area of biologic materials (vaccines, antibiotics, and other such products) a great deal has already been achieved through existing machinery to ensure that knowledge is internationally available and immediately accessible. Perhaps the most important achievements here have been in the international control of infectious disease, in particular, the eradication of smallpox.

It is, however, in the quality of research that the real difficulty lies in the international field. Here we are often dealing with matters of opinion rather than matters of precise measurement. What standards, therefore, do we accept? In many countries individual scientists have their own ideas on what is best. For many clinical scientists the ultimate accolade is to have one's work published in the *Journal of Clinical Investigation*, a reflection of the leadership in scientific and technical matters that the United States at present enjoys. But if the Western European countries and North America agree on particular standards, and there is evidence from the award of Nobel Prizes that they do, do they expect the developing world simply to accept those standards and seek to emulate them? In the field of research on drug treatment such an approach is fraught with both political and scientific difficulties, and we in the West often end up branded as scientific or medical imperialists.

Clinical Research

Clinical science was a development of the Renaissance in Europe; its leading protagonist was William Harvey [2]. Sir Thomas Lewis wrote that clinical science comprised three main streams of investigational activity—the study of living men in health and disease, studies of pathology in the autopsy room, and correlated studies undertaken in lower animals where necessary. Few people recognize that William Harvey used all three of these lines of inquiry in his classical studies of the circulation of the blood. In addition to his beautiful physiological studies in animals and in man, Harvey used clinical observations to illustrate that the blood must circulate [3]. For example, he cited the case of fever and other dread symptoms coming on long after the wound made by a mad dog had been cured, a situation in which he said the contagion had clearly entered the blood stream and in passing through the heart and circulation had polluted distant parts of the body. Lewis thought, as I do, that "De Motu Cordis" represented a "romantic example of scientific exposition unsurpassed in his time and since his time" [2].

How did Harvey's work become internationally known and ultimately accepted, and is the process of dissemination of knowledge any different today? Harvey in fact began in his own country giving demonstrations of his work as many might do at a scientific meeting today. Then he had the opportunity of lecturing on his theories at the Royal College of Physicians of London. Finally he published his work in Frankfurt in Germany in 1628. The

language that he used was Latin, which all scientific men of that era could understand.

Language

What changes have affected clinical science since the time of William Harvey? First, there is the question of language. Latin has now been virtually replaced by English as the *lingua franca* of the scientific world. This means that for all those whose mother tongue is not English, their second language must be English. It equally means, since man is inherently idle in linguistic terms, that those who speak English as their natural language have no incentive to learn other languages. This is resented by those who do not speak English, and there has been a particular problem in the West between the Anglophone and Francophone communities. It is a problem that can only be solved if the Anglophone countries and their educational authorities accept that they have a duty to international understanding to speak at least one language other than English fluently.

Medical Societies

The second development since Harvey's time has been the growth of medical societies. Starting in the 18th century these societies initially were small gatherings of medical men who came together in a city such as Edinburgh or London to discuss problems of mutual interest. This century has witnessed an enormous expansion of the medical society, and in recent years there has been the development of the huge international gatherings that are so popular a feature of the jet-set scientist's life. For scientists, however, the wheel has now turned full circle. Instead of participating in the massive international meeting, held usually at 2- or 4-year intervals, many now opt for the small meeting similar to those of the early medical societies where numbers are limited and where discussion can be free and uninhibited. Such meetings have been the major contribution of the CIBA Foundation in recent years.

Medical Journals

More important to the international scene than the development of the medical societies has been the growth of medical journals. They often started as the proceedings of the small medical societies of the 18th century. In Edinburgh, for example, the *Medical Essays* were published from the 1730's onward, and a group of Edinburgh-trained physicians working in London produced the *Medical Observations and Enquiries* between 1752 and 1784, the first medical periodical in England. The modern medical journal, with its system of peer review, represents the most effective medium for the maintenance of international standards in clinical research. At the same time many English

and American journals, although national, have become international in their scope; this has been not only a reflection of the international use of the English language but also a result of the favorable public and political attitude to the allocation of resources for medical research in the United States, Britain, and the Scandinavian countries.

Health Services

Perhaps the major influence on clinical research during the present century has been the development of health services funded from government sources. Such services vary in quality, and there is a considerable variation in the way in which health is approached in different countries. There are important differences, for example, between the provision of health care in the communist economies of Eastern Europe or the Soviet Union and in the mixed capitalist/socialist economies of Western Europe. In China the development of the barefoot doctor concept, so reminiscent of the medical assistant who was the linchpin of medical care in African countries in the heyday of British imperialism, has had important implications for countries such as Tanzania. More important for medical research has been the increasing demand by politicians who control the finance for relevance in clinical research, an outlook best exemplified by the Rothschild doctrine in Britain and by the Nixon initiative on cancer in the United States. The implications of these developments necessitate constant surveillance by scientists themselves, and it is important that international channels of communication be maintained and encouraged.

Control of Medicines

It is in the field of drug control that the establishment of internationally accepted standards in clinical research is perhaps most attractive. For the moment, however, it seems unlikely that a formal international agency for drug control can be considered desirable if only because the control of drugs is a national rather than an international question and is governed by national law. In the United Kingdom, for example, it is the Medicines Act of 1968 that controls "medicines." Under this act a Medicines Commission was established, together with a series of statutory advisory committees. They include the British Pharmacopoeia Commission and the Committee on Safety of Medicines, which includes subcommittees on Toxicity and Therapeutic Efficacy, Chemistry, Pharmacy and Standards, Biological Materials, Herbal Products, Adverse Reactions, and Antibiotic Substances [4]. Within the Department of Health and Social Security there is a Medicines Division with 230 staff members, including 18 physicians, 51 pharmacists, 19 scientific officers, 4 lawyers, a dental officer, and 120 administrators [5]. This sort of organization is duplicated in many Western countries and is an absolute necessity for administering the national laws relating to drug control. Clearly such an organization can

accept evidence on drug trials from any part of the globe; and, in general, most countries now accept on an international basis properly conducted studies of the effect of drugs on animals.

It is in human studies that there is clearly a continuing need for national rather than international control. The reason for this is not just narrow nationalism but the biological differences that exist between different people in different cultures. A drug given to middle-class shopkeepers in Boston or Glasgow might be metabolized differently than in a group of Japanese individuals of similar status. In human studies there is, therefore, a compelling need for nationally organized trials.

It is, however, important that there be efficient, continuous communication between the national authorities in different countries. In Britain there are formal links between the national agencies and WHO, the European Economic Commission (EEC), and the Council of Europe. Britain is also a signatory of the Convention for the Mutual Recognition in Respect of the Manufacture of Pharmaceutical Products together with a group of other European countries, most of which do not belong to EEC. Of special importance to British officials is the unofficial and informal communication constantly maintained between them and their opposite numbers in the United States and in Canada. There is clearly a vital need for international communication, but there seems at present no particular requirement for an international agency for the control of medicines or clinical trials.

Developing Countries

This state of affairs has important consequences for the developing world. The control of most medicines and their manufacture lies with the developed countries of the Western world. If, therefore, a drug such as a contraceptive pill is produced but banned by a Western country because of an infrequent hazard of thrombosis, does this mean that it should never be used in an African country where spontaneous thrombosis is exceptionally rare? And what about chloramphenicol, a drug with rare but important toxic effects in Western countries, that is widely used in the developing world? It is clearly necessary that the potential benefit of such drugs in such countries must not be jeopardized by a national agency controlling that drug for purely national use in the Western country where it is manufactured. Since the major problem that the world faces today is the relationship between the developed and developing world, this is an area of drug control where discussion in international agencies might be encouraged.

Some in the West may say, what does the developing world have to do with us? The Western countries depend to a very large extent on developing countries for their supply of raw materials. The time will come when Transvaal gold is controlled not by Europeans but by Africans, as has happened to other

commodities around the world during the decolonization of the past half century.

But developing countries are also exciting because they are young and new. One is tempted to conclude by returning to Benjamin Franklin in Paris nearly 200 years ago. Watching Monsieur Montgolfier's hot air balloon rising from the Jardin des Tuileries, a friend asked him of what use it was. Franklin made the immortal reply, "Of what use is a newborn baby?"

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ACCEPTANCE OF FOREIGN DATA BY THE FOOD AND DRUG ADMINISTRATION

J. Richard Crout

The U.S. Food, Drug, and Cosmetic Act requires, among other things, that the clinical trials submitted in support of a new drug application (NDA) be "adequate and well controlled" and be backed up by "full reports of investigations" (case report forms). Published papers alone do not ordinarily provide a sufficient evidentiary basis for approval of newly developed drugs in the United States. Clinical trials intended for submission to the United States but performed in foreign countries must be conducted according to the ethical standards of the Declaration of Helsinki or the laws of the country of origin, whichever provides the greater protection of human participants. All controlled clinical trials meeting these conditions are acceptable by the FDA in support of an NDA.

A number of years ago it would have been unnecessary to consider international standards for the acceptance of foreign data from the viewpoint of the Food and Drug Administration. This situation was changed, however—although it took us a few years to discover this fact—by the 1962 amendments to the Food, Drug, and Cosmetic Act. These amendments mandated a number of policy innovations. For purposes of this discussion, by far the most important was the requirement of adequate and well-controlled trials as the scientific technique by which the evidence necessary for approval of new drugs is to be acquired.

Sixteen years later it is easy to see the outcomes of this legal mandate. On the positive side, there has been a complete transformation in the quality of evidence available for decision-making on new drugs. Simultaneously, the general fields of biostatistics and epidemiology have flowered so that today controlled trials are applied to a variety of therapeutic modalities well beyond drugs. As a result, a sound scientific data base for rational decision-making on therapeutic choices is increasingly being built. This revolution in the quality of evidence available to the medical profession for the practice of rational therapeutics can be appreciated at a glance simply by leafing through a few issues of any modern major medical journal and by comparing the general content of papers with that of 20 years ago. Many things have changed, of course, but one

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of the most striking is the number and quality of therapeutically oriented clinical trials on a wide range of subjects in today's medical literature.

I believe it is now widely recognized that these scientific gains have been purchased, and will continue to be purchased as is always the case for things of value, at some cost. Clinical trials are expensive, and they take time. Because their results may challenge prevailing practices or conventional wisdom, certain trials inevitably provoke controversy. Because they come under the purview of regulatory bodies, they inevitably become the focal point for differences of opinion, and even formal adversarial legal proceedings between industry and Government. In short, they are important and are properly treated as such by all of us.

General Philosophy and Legal Background

I take it as self-evidently desirable that the members of the international research community have common standards relating to clinical research so all valid data from clinical trials will find broad acceptance by the medical profession and by the regulatory authorities. Although this goal is widely recognized among scientists as a worthy one, it has sometimes been difficult to achieve. I would like to outline, therefore, some of the complexities that confound the acceptance of foreign data by the Food and Drug Administration and to review our policies on this issue.

The central factor determining whether a particular trial is acceptable to a drug regulatory agency, and indeed to any scientist, is its scientific credibility. In many subtle ways we each develop our own biases and attitudes on what we find believable, and nations are no different from individual human beings in this regard. The national attitude in any given country on the type of scientific evidence each finds credible comes about from a complex interweaving of scientific and ethical traditions, legal requirements, and national experience. Those of us interested in international drug trials are, in fact, from different countries with different cultures and medical traditions. So it is natural that we should find ourselves sometimes differing on what we find credible as scientific evidence.

The U.S. Food, Drug, and Cosmetic Act requires that, before a new drug can be approved, the new drug application contain "substantial evidence" that the proposed drug is safe and effective for the intended use. The law further defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling."

In addition, the law states that an NDA must contain, among other things, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." The requirement for "full reports" has long been considered by the FDA to mean individual case records or case report forms filled out by the investigator. In short, published papers alone or their equivalent in an NDA are usually *not* considered sufficient to fulfill the "full reports" requirement of the law.

Although many nations now have drug regulatory laws requiring evidence of safety and effectiveness, the specific legal requirements for adequate and well-controlled trials and for full reports of investigations is not a feature of the legislation in countries other than the United States.

There has evolved in the United States a set of drug approval requirements that recognizes two different levels of clinical evidence in support of safety and effectiveness:

1. Studies known as *adequate and well-controlled trials* because they meet the requirements for such trials described in our regulations [1]. These regulations require, among other things, that results attributed to the drug must be compared with a control group "in such a fashion as to permit quantitative evaluation," but these regulations do not require, as alleged by some, that all trials be double-blind placebo-controlled trials. The regulations provide for a no-treatment control, a placebo control, an active treatment control, or a historical control, whichever is scientifically appropriate for the drug under study. Thus, as examples, placebo-controlled trials are typical for analgesics, mild antihypertensives, and dermatological drugs, while active treatment controls are common for antibiotics, and historical controls are typical for general anesthetics, cancer chemotherapeutic drugs, and oral contraceptives. A subset of trials in this category are those known internally at the FDA as pivotal studies. These are trials that are adequate and well controlled as described in the regulations and, in addition, are documented by "full reports" of case records. Pivotal studies are therefore, as the name implies, the most important studies for a fundamental judgment on the effectiveness of a drug.
2. Studies known as *supporting evidence*, which means trials that are not well controlled or contain other information such as anecdotal case reports in which no attempt at control has been made.

For the approval of an NDA for a new molecular entity or the approval of a major new indication, we require the application to contain at least two independent clinical trials considered pivotal in support of safety and effectiveness.

We will also accept a single multiclinic trial as sufficient if at least three separate investigators in the trial have enough patients in their individual clinic to demonstrate a statistically significant result within their own series of patients.

I would emphasize that these are the minimum standards required for a demonstration of effectiveness and of safety over the short term. In addition, we usually also require dose-ranging studies in normal volunteers; studies in pharmacokinetics and bioavailability; evaluation of safety and effectiveness in relatively long-term use (usually at least a year) if the drug is intended for chronic use in humans; studies of the drug by both medical specialists and general practitioners; studies in special patient populations such as children and the elderly; studies in association with other drugs that customarily would be given with the new drug in clinical practice; and studies of comparative claims in relation to other similar drugs, if the manufacturer wants such claims in the labeling. The intent is to assure that every newly marketed new entity has a well-rounded, complete package insert as well as evidence supporting safety and effectiveness. In short, much clinical research conducted under phase III of our regulations is done to provide "adequate directions for use" as well as to support the basic safety and effectiveness of the drug.

We also require that *all* evidence related to the drug be submitted, including incomplete studies and unfavorable studies—a requirement we consider essential because it reveals such interesting information as the investigators who lost interest in the drug or found it to be ineffective, as well as those who completed their studies with favorable results.

A typical new molecular entity has thus been studied at the time of approval by perhaps 20 to 50 investigators in 2,000 to 3,000 patients. In the case of drugs used for the treatment of rare diseases, approval has been granted on the basis of studies in relatively few patients, but this is the exception rather than the rule. Most NDA's are supported at the time of approval by several controlled trials of the pivotal type, additional controlled trials and papers taken from the medical literature, and other information that qualifies as supporting evidence.

It is true that we have accepted on occasion some trials published in the literature as providing "substantial evidence" of safety and effectiveness even though the case records underlying these trials were not available. This has occurred, however, mainly with already marketed drugs where the case records supporting older published studies are literally not available or where the number and quality of independent reports in the literature is sufficiently high that there is little reason to question the validity of the studies.

Approval of a drug or a major new indication on the basis of published papers alone is, however, the exception, not the rule. Our customary approach, and certainly the standard approach with new indications studied under the investigative new drug process, is to require at least two pivotal studies that are well-controlled *and* documented by case reports. This does not mean that we ignore well-controlled studies published in the literature that lack case records

or uncontrolled studies submitted as supporting evidence. But it does mean that such studies are used for somewhat limited purposes, such as the extension of an indication to a new patient population (e.g., children, the elderly) or the providing of new information in the package insert on mechanism of action, metabolism, or adverse effects.

Acceptance of Foreign Data

We are frequently told that the FDA has a long-standing reputation of not accepting, for purposes of new drug approval, clinical trials conducted outside the United States. This is not a correct statement of FDA policy, although I can readily see how this impression of our policy arose.

To set the record straight, I emphasize that the FDA does not have a policy of rejecting foreign studies merely because they are foreign and has never had such a policy. There is no scientific basis for assuming that the quality of clinical research depends on the country in which it is conducted, and FDA policy recognizes no such national distinctions. However, our policy of accepting as pivotal studies only those trials supported by case reports has clearly worked against the acceptance of many well-controlled trials conducted in foreign countries. The issue here, however, is not the country of origin or the scientific quality of the trial, but the degree to which the findings can be documented by case reports.

We are aware that some investigators consider the providing of individual case report forms as, at best, an odious task or, at worst, an improper reflection of their scientific integrity and honesty. This is admittedly a difficult and sensitive problem, but in our experience not an insurmountable one. In fact, objection to this type of documentation tends to disappear as good investigators gain experience with the system. Good scientists will make every effort to assure worldwide acceptance of their work if they understand the reasons.

The FDA requirement for individual case records or report forms derives, regrettably, from unfortunate practical experience. We have simply seen too many studies in which the senior investigator delegated critically important decisions to junior subordinates and failed to report this in the published paper. Case records may reveal that some patients selected for a study did not meet the entrance criteria stated in the protocol, that some failed to take medications on the scheduled dates, that they failed to have essential laboratory studies done at the proper time, that they dropped out or failed to return for visits critical to the study, that they took concomitant medications which might confound the results, or that breakdowns occurred in the randomization or blinding processes. When data are retabulated to take such discrepancies into account, the statistical evaluation of the data and the results of the study may be profoundly altered. Problems of this type are not uncommon in studies submitted to the FDA. Unfortunately, such problems can occur even in studies

conducted by eminent investigators at well-known institutions and in studies sponsored by large, respected drug firms.

It is important to recognize that well-considered protocols and case report forms serve an essential scientific purpose and do not exist merely to fulfill regulatory requirements. Such forms can specifically stimulate the systematic obtaining of essential information on each patient as the study progresses. These forms must be filled out immediately and be monitored continuously by the senior investigator and by the drug firm to assure completeness and accuracy. Anything less cannot properly be considered as well-disciplined scientific research. Clinical trials are inherently complex and error-prone, and their proper execution requires a strong sense of organization and attention to detail. Case report forms, along with a good protocol and effective monitoring, promote the disciplined conduct of a clinical trial. In addition they provide a means of auditing the study later.

To make these policies clear, the FDA has published regulations relating to the acceptability of international clinical research in support of an NDA [2]. These regulations state that adequate and well-controlled trials supported by case records will be accepted on the same basis as such trials conducted in the United States. These trials must be conducted according to the ethical standards of the Declaration of Helsinki or of the laws of the country of origin, whichever provides greater protection to human participants.

In recent years we have been impressed with the quality of information from foreign countries submitted by drug firms under these regulations. Foreign data now constitute the bulk of studies available in many NDA's submitted for approval in the United States. A question frequently asked of the FDA is whether we are prepared to approve an NDA *entirely* on the basis of foreign data collected under these new international research regulations. Our current regulations state "except when the disease for which the drug is being tested occurs with such frequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States"[3]. Although there is no intrinsic scientific reason why certain drugs could not be approved solely on the basis of foreign data, we believe it premature to consider such a policy at this time.

In justifying a requirement for some domestic trials, I can only return to my comments at the beginning of this chapter about credibility. In our modern era of public concern about drug safety, it would simply not be credible for the FDA to approve for marketing a new molecular entity that has never been evaluated by any domestic investigator or practicing physician. It is customary for many countries, especially those with strong drug laws and large markets, to require at least some domestic testing of new drugs before they are approved, and the United States is no exception to this worldwide practice. Until we have considerably more experience, it is likely that most of the foreign drug studies accepted in support of an NDA in the United States will be

phase I and phase II studies, or selected phase III studies. I suspect that some portion of phase III will need to be done domestically for some time to come.

International Harmonization

Finally, I would like to comment on the international harmonization of approval decisions on drugs. If these decisions could be left to scientists and physicians alone, I suspect that international decision-making on drug approvals would be more consistent worldwide than is now the case. However, a variety of other factors enter into decisions besides the scientific evidence at hand. In particular are the marketing desires of the sponsor, the legal standards to be met, and the public procedures to be followed, all of which differ widely among the nations of the world. On the matter of credibility and public acceptance, these legal standards and procedures are not easily translated from one country to another. Nevertheless, those of us in the business of regulation and drug control must make every effort to reconcile such differences. To do otherwise is to promote waste in research and confusion of the drug industry, the medical profession, and the public.

As a suggestion on how to improve harmonization, I believe we must recognize the major reasons for our differences are largely nonscientific. They derive instead from differences in legal standards, attitudes, and the decision-making processes of Government in our respective countries. I would not deny that gains can be made at the technical level from international consensus on such matters as toxicology requirements and methods for the evaluation of safety and effectiveness. But only partial harmonization of approval decisions can result from such technical reconciliation. It is most important that we come to understand in detail each other's laws, each other's decision-making processes, and each other's biases.

References

1. Code of Federal Regulations, Title 21, Food and Drugs, Section 314.111.
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DISCUSSION

George T. Curlin

Chief among the subjects discussed was the problem of how to monitor adverse reactions to new drugs; Dr. Crout was the primary respondent. He was asked if the FDA should not scrutinize the data as carefully from a safety aspect as from the aspect of efficacy in those situations when the information appeared important enough to warrant consideration of relabeling. Dr. Lasagna thought the list of shortcomings in the quality of data, failure to follow protocol, etc., mentioned by Dr. Crout as problems in initial applications were also seen in the restudy of oral hypoglycemics, for example. He asked if the FDA should not scrutinize those firsthand reports with the same intention of looking at the quality of the data on the negative side as on the side of claiming benefits.

Dr. Crout replied that while the University Group Diabetes Program (UGDP) study, which was audited by the FDA, contained deficiencies in the data, the general nature of the incentives for drug companies to pursue possible adverse reactions ensured a fairly complete job of reporting. The FDA, therefore, audits selected studies as a matter of principle. In pursuing this line of inquiry, Dr. Weatherall asked if anyone had any ideas toward developing a national system of reporting adverse drug reactions in general. She acknowledged that workers in the United Kingdom found it difficult to give answers to these questions because it was difficult to state if a reaction were due to the drug or were a general consequence of the illness or the environment. Dr. Crout felt that no one had attacked this problem successfully. Although the United States has a spontaneous adverse drug reaction reporting system similar to that used in the United Kingdom, the drug companies themselves handle the problem to a greater extent in the United States than in the United Kingdom. Therefore, in the United States there is no stable of physicians working for the counterpart of Bill Inman, and as a consequence our contacts with physicians are different from those in the United Kingdom.

Although there are epidemiological surveillance programs of adverse drug reactions in the United States such as the Boston Collaborative Drug Surveillance Program, the Drug Epidemiology Unit at Boston University, and the teratology monitoring activity at the Center for Disease Control (CDC), none of these could be considered a comprehensive national adverse drug reaction system. Because of a network of investigators wherein everyone strives to remain in touch with others, more is happening in this field than the practicing physician knows about. In the United States the reporting system is not so much of a problem as the assembly of reports and the feedback of this information to practicing physicians. Dr. Crout felt the United Kingdom did better

than the United States in this regard, but Sweden probably did better than either country.

The problem of the cost of following up reports of adverse drug reactions was mentioned as being beyond the means of small pharmaceutical firms. This situation makes government participation in the activity more likely. In the United States the FDA and CDC occasionally send physicians to follow up a report of an adverse drug reaction, but Dr. Crout admitted the U. S. Government does not do it very well. Almost all reactions under consideration occur in the first few years of marketing when the drug companies are very active and expert in following up reports. They are required by law to do this and are further stimulated to be aggressive by the threat of litigation, which is a much greater force in the United States than in the United Kingdom. The U.S. Government's job is to understand and deal with the bias often contained in such reports when they are received from the industry, for the information frequently minimizes the problem. Dr. Crout felt the actual legwork is done fairly successfully by industry, and he was not personally in favor of investing more government resources in this area.

Professor Vere suggested the nagging problem of unsuspected adverse drug reactions lay behind all the safety problems under discussion. Most of the reporting schemes depend on the doctor's reporting suspected adverse reactions. In the United Kingdom investigators are beginning to be very uncomfortable with the specter of unsuspected adverse reactions, a feeling increased considerably by the practolol case. Under consideration in the United Kingdom is a plan to initiate a recorded release type of scheme wherein doctors would report all adverse events that might follow exhibition of a drug under surveillance. The crunch in this scheme is the tremendous expense; it is so large that Government will almost surely have to be involved at some point. Dr. Crout agreed the problem of the unsuspected adverse reaction is serious. Although the FDA has looked into this problem extensively and is actively exploring solutions, to his knowledge no one has yet found a cost-effective way to detect previously unsuspected adverse drug reactions (thalidomide and practolol are prime examples). Dr. Crout feels we may be left with considering such reactions a societal cost of new drugs from a cost-effective point of view. If this is the case, the public should be informed.

A member of the panel asked Dr. Crout to respond to Professor Booth's comment in his presentation about the international impact of domestic drug regulations. The highly technically developed countries were noted to bear some responsibility for the availability as well as the development of new drugs that have utility in developing countries. A recent case in point concerned a depot preparation of a progestogen for use as a contraceptive. Although this product has been marketed for years in the United States for use in the management of specific cancers, it was not approved for use as a contraceptive in the United States because of the lack of a suitably identified target population

and its cancer risk, which did not justify use where other contraceptive methods were available. All agreed, however, that its use could be justified in many developing countries where different health and demographic situations pertain. The FDA ruling, therefore, seriously affected the availability of this drug in places where its use could be justified. Dr. Crout acknowledged that regulatory agencies in the highly developed countries have the power to "kill" a drug around the world, so to speak, and one must recognize the fact that safety actions taken by agencies such as the FDA have far-reaching effects. There are times, however, when we do not want the power to operate in this way; and the example cited above may be such a case. Both the United States and the United Kingdom have decided not to approve this drug for use as a contraceptive in their own countries, but it may not be best for this ruling to spread throughout the world. Dr. Crout commented that there is no solution to the problem except to say clearly in public statements and in official comments to organizations such as the World Health Organization that we hope this does not happen. In countries with a population problem, maternal and child health problems, and related problems of limited life expectancy, Dr. Crout said marketing the drug as a contraceptive was justified.

In dealing with the impact of domestic laws on the availability of drugs in the international setting, Dr. Crout pointed out that the new drug law currently under consideration by the Congress contains some interesting provisions bearing on this problem. Under the existing law, a drug cannot be exported from the United States unless it is approved for the same use in this country. Therefore, injectable progestogen cannot be exported for use as a contraceptive. Under the new law, however, an export license can be obtained for any drug if requested by another country. This is a very controversial section of the new law; everyone acknowledges this provision to be a double-edged sword. Although there may be losses as well as gains from this provision of the new law if it is passed, the FDA will try to enforce the new law to produce gains, not losses. A safety aspect override provision is included in the new law, but it is understood the FDA is to exercise its authority under the override provision with careful judgment.

Professor Booth was asked if his term "preventive illness" was not a bit illusive. He had mentioned having enough patients with preventive illness in hospitals to practice on, and this statement in itself indicated the diseases are not, in fact, being prevented although they might be preventable in a theoretical sense. This comment allowed Professor Booth to reemphasize the point that we are being pressured into diverting increasing amounts of scarce resources from acute care into prevention when we do not yet know how to prevent most diseases. Somewhat on the lighter side, Professor Booth commented that there were but two areas in our experience in which preventive efforts were successful: first, in the areas in which legislation was brought to bear on a problem, such as the U.S. legislation of speed limits; and second, by giving 6 years of medical education to someone and encouraging him to stop smoking. He

labeled the rest of our performance in prevention as ludicrous and not very effective, terms which are not necessarily mutually exclusive.

An effort to draft uniform technical information about the side effects and indications for use for drugs promulgated for the developing world, much as they are in the developed world, was one area of consideration for international standards. A factor explaining why many drugs are abused in the Americas is a lack of understanding among practitioners of the guidelines of indications, contraindications, and side effects of drugs imported in quantity by developing countries. The participants did not pursue this suggestion, and there were no other concrete suggestions for international cooperation.

In response to a question about the comparison of time for a new drug to be approved in the United States and the United Kingdom, Professor Lawrence said the mean time in the United Kingdom fluctuates. The mean time for a clinical trial certificate is 3 to 4 months, and the time for a product license is 6 months, assuming all goes smoothly and the application is not returned. The difference in time to obtain approval as a factor in the decision of many drug companies to conduct clinical studies in the United Kingdom was not addressed directly by the participants.

Dr. Crout closed the discussion by supporting the call for joint efforts to place escalating new drug regulations in proper perspective and suggested that the pharmaceutical industry be enlisted in the process. He commented that industry must be more specific than they have been previously in documenting the cost of each regulation. For example, comments to the effect that it requires $55 million to work up a new drug are not likely to produce any rational movement in a complicated process to reduce regulation. Accurate data of the cost of a specific regulation (such as 6-month toxicology data, for example) would be welcomed, however, by reasonable people who can then reconsider the cost and the benefit of such a regulation in the public process.

GENERAL SUMMARY STATEMENT

Kenneth J. Ryan

As I faced the unenviable task of recounting the presentations and exchanges of our 2 days of meetings, a colleague just reminded me: "If this conference was good, it should require no summary, and if it was bad, it shouldn't be summarized." I'll opt for a middle ground and try to highlight a few salient points.

For the most part, ethical concerns in clinical research have in the past been based on the medical practice model and the rectitude of the individual physician-investigator. This has not been completely sound in either theory or practice. Although problems have been few relative to the wide extent of clinical research, when problems have occurred, they have attracted the wide attention of the public and governmental regulatory agencies.

In Great Britain, the experience with thalidomide and the publicity associated with Owen's book, *In Sickness and in Health*, raised the general awareness that all was not well. In the United States, the creation of our national commission was spurred on by concerns over research on aborted fetuses, prison research, psychosurgery, research in mental institutions, informed consent for sterilization, the Tuskegee study of untreated black syphilitics, and the clinical use of such drugs as diethylstilbestrol and medroxyprogesterone. We in the United States had already had our own problems with drug safety many years before thalidomide, resulting in FDA regulatory oversight.

A lesson from these experiences is that when the caretaker is also an investigator, there is at least the semblance of possible conflict. The "paternalistic physician" trying to avoid upsetting patient-subjects has in the past been the sole judge of what to disclose and when to ask for written informed consent. In 1966, the U.S. Public Health Service instituted the requirement that all federally supported research be subject to a peer review committee (institutional review board) with outside representation, as well as an evaluation of risks and benefits and adequacy of the informed consent process. This has left untouched any real surveillance of innovative practice and the unapproved usage of drugs where risks may be higher than in carefully designed research

protocols. In any case, most in the United States agree that the institutional review board function for research has filled an important need and should be maintained and strengthened. It is possible that protection of research subjects by such a review process should be used as a model to protect recipients of medical care rather than the reverse, as was the case in the past.

The "window" referred to by Dr. Levy as the optimal time for testing the safety and efficacy of a medical or surgical procedure is an important concept. On both sides of the Atlantic, medical activities have sometimes crept into practice without adequate justification. One then hears the comment that it would be "unethical" to do a controlled study and deny some patients the benefits of the putative therapy. On the contrary, it was "unethical" to allow activities to creep into practice for which clear risks and benefits were not validated. One need only mention cardiac bypass surgery, hypophysectomy for diabetic retinopathy, or the use of oral hypoglycemic agents to illustrate the point.

In this regard, the United Kingdom, with its National Health Service, is in a better position to support and monitor the actual practice of medicine, innovative therapy, and appropriate clinical research than this country, where the activities are largely in the private sector.

We have had a heated discussion on informed consent. In some instances withholding information from both the subject and relatives had been defended to protect them from undue distress. Although special situations may seem to require this, it is a troubling practice. One should not reinstitutionalize the old paternalism in the guise of being kind and concerned. In the case cited of children with leukemia, the parents may not be able to choose between two forms of imperfect therapy or palliatives, but, at the very least, should they not know that there are no accepted curative therapies (otherwise, why the study?) and that clinical trials will be randomized between two reasonable alternatives with respect to risk and benefit?

In the case of patients in an intensive care unit, should the relatives not know that you are constantly studying ways to deal with emergencies and that alternative forms of care are being studied? Subjects and/or relatives have a right to know that research is being performed. The burden of proof remains on the investigator who withholds information, and with the review board that countenances it. More often than not, information must be adequate to respect the decision-making and autonomy of the individuals involved.

I also deplore the overly technical informed consent documents, but the alternative is clear and relevant disclosure, not its complete absence.

It is impossible to deal with all the issues raised; I highlight as the most important concerns the need for a peer review process for research and practice, the timely validation by appropriate clinical research protocols of innovative therapy before it becomes practice, and adequate disclosure to subjects and/or their relatives. The public we serve and the Government that supports our endeavors deserve no less.

ANALYTIC SUMMATION

Miles Weatherall

On analyzing the proceedings, it seems appropriate to mention some aspects of research with human subjects that have *not* been presented here, but should not be forgotten in taking stock of the subject. We have not talked much about studies on normal volunteers, and we have not heard any volunteers express their opinions about control on their activity. We have also heard no comment from a doctor or research worker from the developing or third world on its problems as they relate to research in human subjects. I will come back to these points, but first let us consider what we have done.

Essentially we have been reviewing our own responsibilities as doctors and research workers. These responsibilities have grown with the growing power of science. They frighten us, and they frighten the community, which needs to be assured that power is well used.

To control this growing power, it is essential for the doctor to retain his sense of responsibility and trustworthiness: for him to be seen as always acting responsibly. It is necessary also to educate the community, so the actions of responsible doctors are understood. A doctor has a responsibility to acquire knowledge as well as to treat: to experiment when he does not know what to do, and not to experiment when he does know. And he should acquire knowledge with the same meticulous care for the individual as he shows in treating the individual patient. Neither the community nor the doctor always sees these simple responsibilities clearly. If this conference has helped to make them more clear and more widely understood, it has served a most valuable purpose.

Some doubts, which I share, have been expressed about "dinosaur" trials. If it needs more than 100 subjects to show an effect, either it is a mighty small effect, or the residual variance is shockingly uncontrolled. Monitoring for rare serious toxic effects is another matter; if an effect occurs in only 0.1 percent of patients, at least 5 to 10 thousand patients must be studied to form an approximate estimate of its incidence and of its severity. But monitoring should be achieved with less formidable cost and use of resources than planned therapeutic trials on the same number of patients.

Doubts have been raised also about informed consent and about ethical committees. The need to restrain unfettered enterprise is not at question, but the processes of amateur advisory agencies and bureaucratic blight are not automatically beneficial. Might it be that setting up a committee is a way of shirking a personal responsibility? There are good and bad reasons for creating a committee, but one who does so should question oneself as to whether it is being done not to give members their rights but to abdicate one's own duties.

Finally, I mentioned some points of view that have not been discussed but might serve as a frame in which to set the work of these useful days. First, about volunteers, are there not a considerable number of well-informed people, particularly working scientists, who will gladly submit themselves to hazardous procedures, knowing the risks of an experiment as well as anyone? What would such courageous and admirable people say if they were prevented from contributing to human welfare by the deliberations of a well-meaning ethical committee? Second, any of us who has studied the subtleties of human interactions ought to ask "How reproducible are the judgments of such committees?" Third, from the developing world a question might come as follows, "How many doctor-hours, doctor-years, are being expended in the niceties of ethical decisions in rich countries, while we have only 1 doctor to cover 10,000 square miles or 80,000 patients?"

I close with these thoughts as part of our collective self-discipline and sense of responsibility to all patients and all people everywhere.

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